UNIVERSITY OF CAPE COAST

LONGITUDINAL DATA ANALYSIS OF SECONDARY PREVENTION OF STROKE IN NORTHERN GHANA

MUSTAPHA ADAMS

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BY

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Thesis submitted to the Department of Statistics of the School of Physical Sciences, College of Agriculture and Natural Sciences, University of Cape Coast, in partial fulfilment of the requirements for the award of Doctor of Philosophy degree in Statistics

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DECLARATION

Candidate's Declaration

I hereby declare that this thesis is the result of my own original research and that no part of it has been presented for another degree in this university or elsewhere.

Candidate's Signature …… Date …….....

Name: Mustapha Adams

Supervisors' Declaration

We hereby declare that the preparation and presentation of the thesis were supervised in accordance with guidelines on supervision of thesis laid down by the University of Cape Coast.

Principal Supervisor's Signature…… Date…….

Name: Prof Nathaniel Howard

Co- Supervior's Signture……. Date……

Name: Dr. Francis Eyiah - Bediako

ABSTRACT

The purpose of the study was to apply an illness-to-death model that will enable us to observe the transition intensities of patients during rehabilitation at some discrete points in time. Finally, discover some risk factors of stroke and estimate the average length of stay of patients at different levels of disease states. A typical review of literature on stroke studies in many research works revealed that none of the articles estimated the possible probabilities of transiting from one disease state to another. To fill this gap, we employed Continuous Time Markov Model (CTMC) in Multi-state Models (MSM) to observe the transition rates of the patients at two monthly intervals for two years. Patient variables are *age, sex, marital status, religion, educational status, occupation, location of the patient, comorbidity type, local treatment, smoking, alcohol intake,* and *hemiparesis*. Results from our study reveal that the male sex, local treatment, and patients free from comorbidity contributed to early recovery in all states than the female sex, with no local treatment and one or more comorbidity. Patients with one or more comorbidity and alcohol intake decline in recovery. The outcome of the transition analysis indicated that patients with mild stroke remain in this state for about ten (10) months before recovery and will never become severe if the patient adheres to treatment. While old and older age groups have some chance of transiting to a less severe state and similar rates of transitioning from mild to a more severe state, the youth have better conditions in these states than these two groups. Further research should be carried out to investigate the role of traditional therapy in stroke rehabilitation.

KEY WORDS

Hazard Rate

Markov Chain

Rehabilitation

State

Stroke Severity

Transition Rate

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DEDICATION

To my loving mother, Miss Faati Adams and my dear wife.

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LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
BI	Barthel Index
CDC	Centre for Disease Control
CNS	Canadian Neurological Scale
CPSS	Cincinnah Prehospital Stroke Scale
CT	Computeried Topography
CTMC	Continuous Time Markov Chain
EKG	Electrocardiogram
FIM	Functional Independence Measure
HBP	High Blood Pressure
MBI	Modified Barthel Index
MRI	Magnetic Resonnance Imaging
NIHSS	National Institute of Health Stroke Scale
PSC	Primary Stroke Centre
SBP	Systolic Blood Pressure
SSA	Sub-Saharan Africa
TIA	Transient Ischemic Attack
TTH	Tamale Teaching Hospital
WHO	World Health Organization
WSO	Word Stroke Organization

CHAPTER ONE

INTRODUCTION

Secondary stroke prevention is one of the most successful goals for all stroke managers and modern medicine. The secondary prevention of stroke entails methods for lowering the risk of recurrence in patients who have previously experienced a stroke (Salter *et al*., 2016). Before looking for treatment for stroke symptoms, most people turn to their general-care physicians or local therapists. Though the incidence of stroke has decreased significantly in some industrialised countries because of population-wide high blood pressure control initiatives, it has increased in underdeveloped nations like Ghana (Amuah, 2019). The stroke burden is compounded by the high rate of morbidity, which results in around 50% of stroke survivors in Ghana being permanently incapacitated (Amuah, 2019).

Although Ghana has implemented prophylactic measures to control the disease, the complexity of stroke treatment and recovery is growing due to many morbidities and socioeconomic problems (Nelson *et al*., 2018). In this research, we looked into the effectiveness of secondary prevention therapies on the severity of stroke among survivors in Ghana over time. Using a multistage modelling approach, we retrived patients' records (age, sex, educational status, marital status, time spent before admission, pre-treatment, severity state, and lifestyle) from the Tamale Teaching Hospital. The purpose of this research is to develop an illness-to-death model that will enable us to observe the transition intensities of stroke patients on rehabilitation at some discrete points in time. We aim to discover some risk factors that influence recovery and the effect of comorbidity. We also aimed at determining the

prevalence of some comorbidities in stroke patients and examining their predictive values in the various disease states. Finally, we examined the average length of stay of patients in the various transient states. This will inform medical personnel on the duration of treatment for stroke patients and other possible costs necessary for treatment.

Background to the Study

A stroke happens when there is a decrease or interruption in the blood supply to the brain. When this occurs, the brain cells start to die due to insufficient oxygen or nutrients (Maxwell, 1983). One of the risk factors for stroke is hypertension, which, along with diabetes mellitus, smoking, inactivity, obesity, growing age, and diet, is responsible for over eighty percent (80%) of all stroke cases (Edzie *et al*., 2021). Patients who survive a stroke are at high risk of recurrent stroke (Elkind, 2009). According to Donkor (2014), stroke is responsible for approximately six million deaths every year and thereby claims more lives than HIV/AIDS, tuberculosis, and malaria put together.

About 6.5 million people worldwide died from a stroke in 2013, making it the second-leading cause of death after ischemic heart disease. In the United States, stroke was the fifth-leading cause of death (Nawata, 2020), with approximately eight hundred thousand (800,000) people having a stroke each year (Nawata, 2020). In the United States, a stroke typically occurs every 40 seconds, and on average, a stroke-related death occurs every 4 minutes. (Benjamin *et al*., 2017). The assessment of the global burden of disease for the years 2002–2020 shows rather unwelcoming projections of the worldwide burden of stroke.

There are not many statistics on stroke mortality. Stroke is one of the leading causes of death in middle, and low-income nations, and this fact has been established in recent years. Approximately eighty-seven percent (87%) of all deaths by stroke occur in these countries. Community-based studies in Sub-Saharan Africa (SSA) show that stroke is the cause of five to ten percent (5%–10%) of all deaths (Donkor, Tetteh-Quarcoo, Nartey & Agyeman, 2012).

Stroke is one of the top five causes of death in Ghana and one of the most common medical conditions to be treated in hospitals (Kobina *et al*., 2021). Stroke rose from the eleventh cause of early death in 1990 to the seventh cause in 2010 (Feigin *et al*., 2014). Additionally, stroke was the most prevalent non-communicable condition to cause death between 1990 and 2010. Moreover, the prevalence of fatal stroke cases in the nation is significant (Donkor, Tetteh-Quarcoo, Nartey & Agyeman, 2012; Sanuade, Agyemang, de-Graft Aikins, Agyei-Mensah, & Agyemang, 2013). A study has further revealed that the main risk factors for stroke in Ghana are hypertension, diabetes, obesity, ageing, and plasma levels of homocysteine (Donkor, Tetteh-Quarcoo, Nartey & Agyeman, 2012; Sanuade *et al*., 2006), and that between 60% and 90% of strokes in the country are hemorrhagic (Sanuade, Dodoo, Koram, & De-Graft Aikins, 2019). Stroke is said to have been among the top three causes of death in Ghana (Donkor, Samue & Albert, 2017). Unrestrained blood pressure is the most consistent cause of stroke in Ghana. It contributes to about seventy percent (70%) of all cases, and about forty percent (40%) of stroke patients who seek treatment do not survive. With the growing incidence of uncontrolled hypertension, there has been a sharp rise in the number of stroke patients in Ghana (Sanuade *et al*., 2019).

Statement of the Problem

Globally, stroke is a healthcare problem that is common, serious, and incapacitating (Warlow *et al*., 2008). It is a serious health concern for both young people and the elderly. This is because it impacts not only physical impairment but also causes depression, incapacity, and stigmatisation (Pan, Song, Lee, & Kwok, 2008). Such changes have a potential impact on the health-related quality of life of stroke survivors. The psychological effects of stroke survivors require some lifestyle adjustments because the impact of a stroke on a patient is typically frightening and frequently joyless (Donkor, 2014).

Secondary prevention is considered an important aspect of stroke therapy, focusing on the prevention of future events such as walking, functional skills, or swallowing disorders (Goldberg & Berger, 1988). Goldberg and Berger emphasized the significance of secondary stroke prevention in patients with antithrombotic brain infarction and the reduction of major vascular events, including myocardial infarction (Goldberg & Berger, 1988). In stroke rehabilitation, the disease's status typically consists of a series of mutually exclusive states (Goldberg & Berger, 1988). The transition between any two states can provide important statistics about the disease's severity. Such data can be analysed through longitudinal studies, where patients' disease states are measured over time during follow-up visits. Patients are normally scheduled by their medical officers for successive visits. However, patients do not always follow through with scheduled appointments due to practical reasons associated with unevenly spaced follow-up time points (Huang *et al*., 2015).

Additionally, the full course of the disease is typically difficult to monitor. A patient's disease history is continuous over time in terms of condition changes. The patient's current condition is determined, but the actual changes between two consecutive visits are not observed; if any occur, they occur at unknown times, and the state occupied during the interval is also unknown. Multi-state models (MSM) are a class of modelling techniques specifically developed to analyse state transition over time and have been successful in monitoring HIV/AIDS (Uebelacker, 2017), diabetic retinopathy, cancer, asthma, cirrhosis of the liver progressing to HCC (Bartolomeo, Trerotoli, & Serio, 2011), and chronic obstructive pulmonary disease (COPD).

Considering the high public burden of stroke in Ghana, there is scarcely any detailed research on the rehabilitation and severity of stroke among survivors. Very few stroke studies seem to have concentrated on risk factors, mortality, morbidity, case fatality rate, and the burden of stroke. There is a single study on the quality of life of stroke survivors in southern Ghana, ignoring the severity of stroke among survivors. The few researchers that studied stroke severity among survivors (Jones *et al*., 2000; Rost *et al*., 2016; Williams, Yilmaz, & Lopez-Yanez, 2000) conducted prospective studies on predictors of initial stroke severity without considering the exact transition times between disease states. This study seeks to investigate the efficacy of secondary prevention therapies on the severity of stroke among survivors in Ghana over time using continuous time Markov chains (CTMC) in multi-state modelling.

Research Objectives

General Objective

This study's primary goal is to examine the efficacy of secondary prevention therapies on the severity of stroke among survivors in Ghana over time.

Specific Objectives

The specific objectives of the study are to:

1. Determine some factors that influence stroke severity.
2. Assess the impact of comorbidities on patients.
3. Assess how the initial prescription, continuation, and cessation of appropriate secondary prevention impact survivors.
4. Evaluate the transition rates of stroke severity, vascular events, and death up to two years after the index event.

Research Questions

1. To what extent do age, alcohol intake, gender, ethnicity, social deprivation, living circumstances, independence in activities of daily living (ADL), and comorbidity influence stroke severity?
2. Once started, our treatments continued or stopped; what factors are associated with this?
3. How do initial prescription, continuation, and cessation of appropriate secondary prevention impact survival and further events over follow-up?
4. Which components of secondary prevention are most important for the reduction of mortality or subsequent vascular events?

Significance of the Study

The effects of stroke on patients are frequently surprising and depressing, necessitating significant changes in their way of life and psychology. It renders the survivors physically and functionally deficient and unable to contribute their maximum to the country. To curtail this situation, some factors need to be identified that could be used to monitor and predict disease progression. This research seeks to provide information on how stroke rehabilitation is done at the Tamale Teaching Hospital (TTH). It will also unearth the characteristics of patients at various transition states after the index stroke event and identify markers of comorbidity treatment that influence secondary prevention.

The work will also provide the best models to unearth factors that impact the severity of stroke among patients, indicate possible probabilities of disease progression, and underpin recommendations for the implementation of secondary prevention guidelines at the practice or hospital level, which will directly impact patient outcomes in Ghana and beyond.

Delimitation

This research is driven research; it requires data from an institution (Tamale Teaching Hospital). This hospital is a referral centre that offers a range of medical services to the residents of the Northern, Upper West, Upper East, North East, and Savannah regions. We identified data problems for which known methods (MSM) would be used to analyze and enhance insight into the data and its generation mechanism. Homogenous Continuous Time Markov Chain (CTMC) was used to determine disease progression at the various states termed *discontinued*, *stopped*, *dead*, and *end period*.

The study adopted retrospective data from a cohort from January 1, 2014, to December 31, 2019. The study participants are comprised of stroke outpatients from the physiotherapy clinics and the Medical Unit of the Tamale Teaching Hospital (patients who have recovered from past cerebrovascular accidents and are receiving treatment).

Limitations of the Study

This study population does not cover the entire country. It covers only the Northern territorial part of Ghana. Patients were not contacted directly for information, but rather, data were retrieved from their database in TTH. Follow-up was mainly done by the medical officers. Avalaible sample size of 37 was used for the study. The study did not also include simulation in the analysis and because of the small sample size, hence the study did not check for model robustness and only goodness-of test was performed to validate the model.

Organisation of the Study

In Chapter One, we briefly described how we sourced our data and also described data. This was followed by background information on the incidence of stroke in Ghana. To carry out this research, we need to identify real problems among stroke patients on follow-up. We also set up research objectives and questions to enable us to get a solution to the research problem. We clearly stated the significance of the study and its relevance to this research. The scope and delimitations for this research were outlined, including limitations, the organisation of the thesis, and a summary in Chapter One.

We introduced Chapter Two with definitions of terms and concepts (including secondary prevention of stroke, stroke symptoms in men and women, types of strokes, risk factors for stroke, prevention of stroke, stroke treatment, and a stroke measurement scale). We did some reviews of research findings on comorbidity and rehabilitation of stroke, stroke dynamics and stroke studies in Ghana, and predictors of stroke severity. We were able to identify some gaps and suggest ways of addressing these gaps among some of the reviewed papers: Chang *et al*. (2006), Gadidi *et al*. (2010), Jones *et al*. (2000), Lemmens, 2018, Rost *et al*. (2016), and Ziegler *et al*. (2008). Finally, the theoretical and conceptual frameworks of longitudinal studies were explained.

In Chapter Three, we described our study design (longitudinal design). We also outlined both the study population and data set. This is followed by the description of the theoretical concepts of our main models: CTMC, homogeneous Continuous Time Markov Chain This section explains how the transition occurs between two or more states. We also narrated how to use the MSM package in R to model CTMC.

We began Chapter Four with some introductory notes on the reasons for using CTMC in MSM to observe the transition rates of stroke patients at TTH. Our first output shows the descriptive statistics of stroke patients in rehabilitation. The next topic in this chapter is the display of transition frequency distribution. Included in the output were the baseline transition rates and the various covariates' transition intensities. The average length of stay in the various states was also displayed using the mean sojourn time model. To assess the goodness of fit of our CTMC for each state, we used the graphical

comparison of the observed versus the expected number of patients in each state at various time points (Cassarly, Chimowitz, Palesch, & Surgery, 2020). Survival plots indicating the number of people in the various states were used to check the accuracy of our main model. Finally, we discussed our results based on our findings.

The summary, conclusion, and recommendations were done in the last chapter (Chapter 5). We provided suggestions for further research using CTMC that included misclassifications of transition states.

Chapter Summary

Globally, measures for secondary prevention of stroke have been outlined for the successful management of stroke. Developed countries are experiencing a decline in the incidence of stroke while developing countries like Ghana continue to see a rise in the incidence rate of stroke. One of the top five killers and a leading cause of hospital admissions is stroke (Kobina *et al*., 2021). There is very little thorough research on rehabilitation and stroke severity among survivors due to the high prevalence of stroke in Ghana.

The state of the disease is usually composed of a series of mutually exclusive states. The transition between any two states can provide important information about the disease's severity. Such data can be analysed through longitudinal studies, where patients' disease states are measured over time during follow-up visits. Patients are normally scheduled by their medical officers for a subsequent visit (Huang *et al*., 2015). Usually, one cannot fully observe the entire course of the disease. The state transitions in a patient's disease history are continuous over time. The current condition of the patient is known, but the transitions between the two subsequent visits, if any, occur

at unknown times, and the state occupied during the interval is also unknown. We would use multi-state models (MSM) (a class of modelling) techniques to specifically develop and analyse state transition over time.

Homogenous Continuous Time Markov Chain (CTMC) was used to determine disease progression at the various states: discontinued, stopped, dead, and end period. The study adopted prospective data from a cohort from January 1, 2014, to December 31, 2019, from TTH. This exercise was done within the five regions in the northern half of the country. The research will provide information on how the rehabilitation of strokes is done at the Tamale medical facility.

CHAPTER TWO

LITERATURE REVIEW

Introduction

In Chapter Two, we provide an overview of the literature on stroke symptoms, types of stroke, some concepts of stroke, stroke measurement scales, and the characteristics of longitudinal studies. We also review previous research on stroke severity and identify some gaps in related work. We finally suggested ways in which we intend to fill these gaps. The theoretical and conceptual frameworks have been explained.

Definition of Terms and Concepts

Stroke

A stroke happens when a blood vessel in the brain bursts and bleeds or when the blood supply to the brain is cut off. The break or obstruction prevents blood and oxygen from getting to the brain's tissues (Maxwell, 1983). The brain tissue and cells suffer damage and start to die without oxygen within minutes. Stroke is the fifth-leading cause of mortality in the United States as of 2017, according to the Centres for Disease Control and Prevention (CDC). More than 795,000 Americans experience a stroke each year (Maxwell, 1983).

Secondary Prevention of Stroke

Secondary prevention

This clinical procedure aims to lower the risk of a subsequent vascular event in people who have previously had a stroke, angina, transient ischemic attack, myocardial infarction, heart failure, irregular heartbeat, structural heart disease, vascular cognitive impairment, or peripheral vascular disease (Yusuf *et al*., 2014). Recommendations for secondary prevention are centred on the

risk factors that have been shown to reduce recurrence and lengthen survival after vascular conditions, as well as responsiveness to the standard of living (prudent diet, reduced sodium intake, increased level of daily activity, maintaining best body weight, quitting smoking, and controlling alcohol intake) and management of medical conditions like hypertension, dyslipidemia, and heartbeat management (Yusuf *et al*., 2014).

Stroke Symptoms

Brain tissue is harmed by a reduction in blood flow to the brain. The bodily functions regulated by the brain injury exhibit stroke symptoms.

Stroke signs include:

1. Paralysis
2. On one side of the body, one may experience weakness or numbness in the arms, legs, or face.
3. A problem with speech comprehension or speaking
4. Confusion
5. Speech blending
6. Vision issues, such as double vision, blacked-out vision, or difficulty seeing in one or both eyes
7. Walking difficulties
8. Loss of balance or coordination
9. Dizziness
10. Sudden, severe headache with no apparent explanation

Any stroke victim needs to see a doctor right away. It's critical to seek treatment right away to avoid the following outcomes:

1. Brain injury

2. Long-term impairment
3. Death

Symptoms of Stroke in Women

1. Throughout their lifespan, women are more likely than men to have a stroke. While certain stroke symptoms are the same for both sexes, some are more prevalent in women. Stroke symptoms that are more prevalent in women are:
2. Feeling queasy or sick
3. Hallucination
4. Pain
5. Weaknesses all around
6. Breathing difficulties or shortness of breath
7. passing out or becoming unconscious
8. Seizures
9. Disorientation, confusion, or a lack of attentiveness
10. Sudden alterations in conduct

Symptoms of Stroke in Men

It is crucial to recognise a stroke as soon as possible because women are more likely than men to die from one. For men, a stroke is the seventh most common cause of death. Males are more likely than females to have a stroke when they are younger and are less likely to die (Agyeman *et al.*, 2006). However, some stroke symptoms and indicators are common to both men and women. These comprise:

1. An unbalanced smile or facial drooping on one side
2. Speech impairment and communication difficulties

3. One-sided muscle weakness in the arms or body

Although some symptoms may vary between men and women, it is crucial for both to recognise a stroke early and seek medical attention.

Types of Strokes

Transient ischemic attack (TIA), ischemic stroke, and hemorrhagic stroke are the three primary types of stroke (National Institute of Neurological Disorders and Stroke, 2021). TIA is also referred to as a warning or mini-stroke and is caused by temporary restriction of blood flow to the brain (National Institute of Neurological Disorders and Stroke, 2021). The symptoms of TIA and blood clot are temporary (National Institute of Neurological Disorders and Stroke, 2021).

Ischemic stroke occurs when a blood clot obstructs blood flow to the brain, typically due to atherosclerosis, the accumulation of fatty deposits on the inner lining of a blood vessel (American Heart Association, 2021). The fatty deposits may fragment and obstruct blood flow to the brain, similar to how a blood clot restricts blood flow to a section of the heart during a heart attack (American Heart Association, 2021). Embolic stroke occurs when a blood clot travels from one part of the body to the brain during an ischemic stroke, and approximately 15% of strokes are caused by embolic stroke due to a condition called atrial fibrillation, where the heart beats irregularly (American Heart Association, 2021).

An ischemic stroke, also known as a thrombotic stroke, results from a blood clot developing in a blood vessel in the brain, and the clot resolves on its own without medical intervention (National Institute of Neurological Disorders and Stroke, 2021). Hemorrhagic stroke occurs when a blood vessel

in the brain ruptures or breaks, causing bleeding into nearby tissues (American Heart Association, 2021). Hemorrhagic stroke can occur due to various reasons, such as an aneurysm, arteriovenous malformation, or extremely high blood pressure (American Heart Association, 2021)

Risk Factors for Stroke

One is more prone to stroke due to certain risk factors. The National Heart, Lung, and Blood Institute states that your risk of having a stroke increases as your risk factors increase. Stroke risk elements include:

Diet

A poor diet that raises the risk of stroke is one that is high in:

1. Salt-saturated fats
2. Trans fats
3. Cholesterol

Lack of exercise or inactivity

This can also increase the likelihood of having a stroke.Numerous health advantages come from regular exercise. Adults should engage in at least 2.5 hours of aerobic activity per week, according to the CDC. This can just mean going for a few quick walks each week.

Alcohol use

Drinking too much alcohol raises one's risk of having a stroke. Moderation should be used when consuming alcohol. That entails a daily limit of one drink for women and two for men. Excessive amounts of anything can result in higher lipid and blood pressure levels, which can lead to atherosclerosis.

Use of tobacco products

Using tobacco products increases the risk of stroke since they can harm blood vessels in addition to the heart. Smoking increases the risk of stroke because nicotine use causes an increase in blood pressure.

Personal background

Certain personal risk factors for stroke are out of a person's control. A person's risk of stroke can rise due to a variety of causes, such as:

Family history

Some families are more likely to suffer from strokes as a result of inherited medical conditions, including high blood pressure.

Sex

While both men and women can experience strokes, women are more likely than men, according to the CDC, to experience them across all age categories.

Age

A stroke is more likely to occur in elderly people.

Health history

The risk of stroke is connected to particular medical problems.

These consist of:

1. A prior TIA or stroke
2. High blood pressure
3. High lipid content
4. Heart conditions such as coronary artery disease
5. Abnormal heart valves
6. Excessive heart tissue and irregular heartbeats

7. The sickle cell disorder
8. Diabetes

Stroke Diagnosis Tests

To help a doctor establish whether a patient has had a stroke or to rule out another ailment, he or she may undergo a variety of blood tests. These tests comprise testing for:

1. A person's blood sugar levels
2. If someone is infected
3. The person's platelet counts
4. How quickly one's blood clots

CT scan and MRI

Both computerised tomography (CT) and magnetic resonance imaging (MRI) scans can be employed. The MRI will assist in identifying any damaged brain tissue or brain cells. Any bleeding or injury to the brain will be visible in a thorough and clear image of the person's brain provided by a CT scan. It might also reveal additional brain abnormalities that could be the source of the symptoms (Kumar & Juweid,2020).

EKG (or ECG)

An electrocardiogram (also known as an EKG or ECG) can be performed. During this examination, the heart's electrical activity is recorded along with the heartbeat's rhythm and speed. It can reveal whether a person has any cardiac abnormalities, including atrial fibrillation or a previous heart attack, that may have contributed to a stroke.

Angiogram of the Brain

Cerebral angiography is a different test that could be requested to find out if someone has had a stroke. It provides a thorough view of one's neck and brain arteries. Blockages, as well as clots that could have triggered symptoms, can sometimes be shown by the testing.

CT Scan of the Carotid

The carotid arteries, which carry blood to the face, neck, and brain, contain fatty deposits (plaque), which can be seen during a carotid ultrasound, also known as a carotid duplex scan. Additionally, it might reveal whether the carotid arteries are obstructed or constricted.

The echocardiogram

The origin of clots in the heart can be determined through an echocardiogram. One may have experienced a stroke as a result of these clots moving to their brain.

Treatment of Stroke

Recovery from a stroke depends on a thorough medical assessment and quick treatment. Time missed means brain damage, according to the American Heart Association (2017). As soon as it is apparent that someone is having a stroke, or if a person suspects that a loved one is experiencing a stroke, they must immediately take the victim to a health care facility.

Treatment for strokes is based on the type of stroke

A blood clot or other obstructions in the brain are the causes of an ischemic stroke and a transient ischemic attack (TIA). Because of this, they are generally treated using methods that are comparable, such as:

Antiplatelet and anticoagulants

The first line of defence against the effects of a stroke is frequently over-the-counter aspirin. After stroke symptoms start, anticoagulant and antiplatelet medications should be taken 24 to 48 hours later.

Clot-breaking drugs

Blood clots in the arteries can be removed using thrombolytic medications. It will halt the stroke and lessen brain damage. One such medication, tissue plasminogen activator (tPA), also known as Alteplase IV r-tPA, is regarded as the gold standard in treating ischemic stroke. If during the first 3 to 4.5 hours after the onset of stroke symptoms, it efficiently dissolves blood clots, People who may have a tPA injection have a higher chance of recovering from a stroke and a lower chance of developing any long-term disabilities.

Mechanical Thrombectomy

A catheter is inserted by the doctor during this procedure into a sizable blood vessel inside the patient's head. The clot is then extracted from the vessel using a device. The best chance of success for this procedure is if it is done six to twenty-four hours after the stroke starts.

Hemorrhagic stroke

Different therapeutic approaches are needed for strokes brought on by brain bleeds or leaks. Hemorrhagic stroke can be treated by:

Medications

Inducing a blood clot is the goal of treatment for a hemorrhagic stroke as opposed to an ischemic stroke. As a result, medicine to counteract any blood thinners taken may be provided to the patient. Additionally, medications

that can lower blood pressure, lower brain pressure, stop seizures, and prevent blood vessel constriction may be administered.

Coiling

A doctor performs this operation by directing a lengthy tube to the site of bleeding or weak blood vessels. The weak spot in the artery wall is then treated with a coil-like device. This lessens bleeding by obstructing blood flow to the location.

Clamping

A ruptured aneurysm or one that has ceased bleeding may be found by a doctor during imaging examinations. A tiny clip may be inserted at the aneurysm's base by a surgeon to stop further bleeding. By cutting off the blood flow, this avoids the possibility of a blood vessel breaking or fresh bleeding. A doctor may perform surgery to clip an aneurysm and stop further bleeding if they discover that an aneurysm has burst. The strain on the brain after a significant stroke may also require a craniotomy. In addition to providing emergency care, healthcare professionals will offer recommendations for stroke prevention.

Stroke Medications

Strokes can be treated with a variety of drugs. The kind of stroke one gets has a significant impact on the medication a doctor recommends. Some drugs work to prevent a stroke from happening again, while others try to prevent a stroke from happening in the first place. The most typical stroke treatments include:

Tissue plasminogen activator (TPA)

This emergency drug might be given to dissolve a blood clot that is the cause of a stroke. It must be administered within 3 to 4.5 hours of the onset of stroke symptoms because it is the only drug that can manage this at the moment. To lower the chance of complications from the stroke, this medication is injected into a blood vessel so that it can begin working as soon as possible.

Anticoagulants

These medications reduce the ability of blood to clot.Warfarin is the most popular anticoagulant (Jantoven, Coumadin). These medicines may be recommended to prevent a stroke or after an ischemic stroke or transient ischemic attack (TIA) because they can stop blood clots from becoming larger than those that already exist.

Antiplatelet drugs

These drugs work to prevent blood clots by making it more difficult for platelets in the blood to adhere to one another. The two most widely used antiplatelet medications are aspirin and clopidogrel (Plavix). They are useful in ischemic stroke prevention and crucial in subsequent stroke prevention. Only those with a low risk of bleeding and a high risk of atherosclerotic cardiovascular disease, including heart attacks and strokes, should take aspirin as a preventive medicine.

Statins

Statins are among the most often recommended medicines because they help control elevated blood cholesterol levels. These medications stop an enzyme from being produced that can transform cholesterol into plaque, the

fatty, gooey material that can accumulate on the walls of arteries and lead to heart attacks and strokes. Statins including rosuvastatin (Crestor), simvastatin (Zocor), and atorvastatin are frequently used (Lipitor).

Blood pressure drugs

A person's arteries may begin to tear apart due to high blood pressure. A stroke may result from these fragments obstructing arteries. Therefore, lowering high blood pressure can aid in reducing the risk of stroke. Depending on factors including your health history and risk, doctors may recommend one or more of these medications to treat or prevent a stroke. Strokes can be treated and prevented with a variety of drugs.

Stroke Prevention Techniques

Living a healthy lifestyle is one action you may take to help prevent stroke. Among these are the following actions:

Quit smoking

Quitting smoking now will reduce a smoker's risk of having a stroke.

Consume alcohol in moderation.

Alcohol abusers need to make an effort to cut back on their consumption. Blood pressure can increase after drinking alcohol.

Keep the weight down

A healthy weight should be maintained. One's risk of stroke rises if they are overweight or obese. This will aid in weight management.

Stay physically active

This will assist in preserving a healthy weight as well as lowering blood pressure and cholesterol levels.

Get checkups

Keep an eye on your health. This calls for routine checks and maintaining contact with your physician. To control your health, make sure to follow these steps: Obtain a blood pressure and cholesterol assessment. Discuss changing your lifestyle with your doctor. Talk to your doctor about your pharmaceutical options. Take care of any heart issues you may have. Get your diabetes under control if you have it. All of these actions will help you get in better condition so you can prevent stroke.

Stroke Measurement Scales

Barthel Index

Ten (10) personal activities are covered by the Barthel, including feeding, personal toileting, bathing, dressing and undressing, getting on and off a toilet, controlling the bladder and bowels, moving from a wheelchair to bed and back, walking on a level surface (or propelling a wheelchair if unable to walk), and climbing stairs. An observer, such as a therapist, can complete the three-item original index in 2 to 5 minutes. Each item is rated according to whether the patient can complete the task without assistance, with some help, or needs assistance based on observation (0 = unable, 1 = needs assistance, 2 = independent). To get a number on a scale of 100 points, the final score is multiplied by 5. Scores of 0 to 20 are considered to indicate "complete" dependency, 21 to 60 "severe" dependency, 61 to 90 "moderate" dependency, and 91 to 99 "slight" dependency, according to the proposed standards for interpreting Barthel scores. Most studies use a cutoff point of 60 or 61.

Table 1: The Barthel Index

Index Items	
Bowels	Toilet use
0 = Incontinent or needs enemas	0 = Dependent
1 = Occasional accident (once/week)	1 = Needs some help
2 = Continent	2 = Independent
Bladder	Transfer (bed to chair and back)
0 = Incontinent, or catheterized and unable to manage	0 = Unable, no sitting balance
1 = Occasional accident (maximum once per 24 hours	1 = Major help (1 or 2 people), can sit
2 = Continent (for over 7 days)	2 = Minor help (verbal or physical)
	3 = Independent
Grooming	Feeding
0 = Needs help with personal care	0 = Unable
1= Independent (including face, hair, teeth, shaving)	1 = Needs help cutting
	2 = Independent
Dressing	Mobility
0 = Dependent	0 = Immobile
1= Needs help, but can do about half unaided	1 = Wheelchair independent, including corners, etc.
2 = Independent (including buttons, zips, aces etc.)	2 = Walks with help of one person (verbal or physical)
	3 = Independent (but may use any aid)
Feeding	Stairs
0 = Unable	0 = Unable
1 = Needs help, eg. cutting	1 = Needs help (verbal or physical)
2 = Independent	2 = Independence

(Quinn *et al*., 2011)

The Cincinnati Prehospital Stroke Scale (CPSS)

In a pre-hospital context, this approach is used to identify probable strokes. Three symptoms are examined for any unusual results that would indicate the patient has had a stroke. If any of the results from the three tests are abnormal, the patient may be having a stroke and needs to be taken to the hospital as soon as possible. The University of Cincinnati Medical Centre's 1997 development of the National Institutes of Health Stroke Scale for pre-hospital use formed the basis for the development of the CPSS.

Abnormal: One side moves differently from the other.

1. Arm drift: Have the patient close their eyes and extend their arms for about 10 seconds with their palms up. The patient should respond, "You can't teach an old dog new tricks," if one arm is not moving or is drooping.
2. Abnormal: The patient cannot talk, slurs words, or uses improper words.
3. Transport Requirements to a Primary Stroke Centre (PSC). If the base station suspects an acute stroke of less than six hours' length based on any of the following, patients without detectable stroke symptoms may be taken to a PSC:
    1. A sudden and enduring change in consciousness
    2. A sudden, intense headache (particularly when there is vomiting and a systolic blood pressure of 200 or below)
    3. A serious and unexpected loss of equilibrium

National Institutes of Health Stroke Scale (NIHSS)

As a study tool for assessing the severity of strokes, the National Institutes of Health Stroke Scale (NIHSS) was created. The NIHSS is now the industry standard for clinical stroke assessment and measurement, moving beyond the realm of academic research. The NIHSS is a useful tool for determining the severity of a stroke at first and for continuous evaluations that look for changes in the patient's condition that can be taken to improve their health.

Table 2: National Institutes of Health Stroke Scale (NIHSS)

Instruction	Scale Definition
1a. Level of Consciousness: Alert; keenly responsive. 1 = Not alert; but arousal by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend.. 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and are flexic	2. Best Gaze: 0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.
1b. LOC Questions: (The patient is asked the month and his/her age) 0 =Answers both questions correctly. 1 = Answers one question correctly. 2 =Answers neither question correctly.	3.Visual: Visual fields (upper and lower quadrants) 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).
1c. LOC Commands (The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used).	1. Facial Palsy: Ask or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes 0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling).

Table 2:Cont.

0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly	2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides.
1. Motor Arm The limb is placed in the appropriate position: extend the arms 0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees.. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion, explain 5a. Left Arm ……. 5b. Right Arm ……..	2. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine) 0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion, explain: 6a. Left Leg …….. 6b. Right Leg ……
7.Limb Ataxia**:** This item is aimed at finding evidence of a unilateral cerebellar lesion. 0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain	8 Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient 0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.
9 Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas	10**.** Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. 0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is

Table 2:Cont.

expressed or form of expression. 2 = Severe aphasia; all communication is through fragmentary expression 3 = Mute, global aphasia; no usable speech or auditory comprehension.	so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier, explain

1. Extinction and Inattention (formerly Neglect):

Sufficient information to identify neglect may be obtained during the prior testing.

0 = No abnormality.

1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.

2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

(Côté *et al*., 1989)

Face Arm Speech Test (FAST)

The acronym FAST is used as a mnemonic to make it easier to recognise and respond to the needs of someone who is having a stroke. The letters in the acronym stand for face drooping, arm trembling, speech problems, and time to contact 911.

1. Facial drooping: a part of the face that is drooping and difficult to move, usually only on one side. This can be detected by a crooked smile.
2. Arm weakness: the difficulty in fully raising an arm or the inability to grasp or squeeze (for example, someone's hand).
3. Slurred speech: trouble repeating even simple sentences like "The sky is blue" or an inability or difficulty to interpret or generate speech are all examples of speech issues.

Global Prevalence of Stroke

According to disability-adjusted life years lost (DALYs), stroke continues to be the second-leading cause of death and the third-leading cause

of death and disability combined worldwide.The estimated global cost of stroke is over US$721 billion (0.66% of the global GDP). From 1990 to 2019, the burden (in terms of the absolute number of cases) increased substantially (70.0% increase in incident strokes, 43.0% deaths from stroke, 102.0% prevalent strokes, and 143.0% DALYs) (WSO, 2022), with the bulk of the global stroke burden (86.0% of deaths and 89.0% of DALYs) residing in lower- and lower-middle-income countries (LMIC). This World Stroke Organisation (WSO) Global Stroke Fact Sheet 2022 provides the most updated information that can be used to inform communication with all internal and external stakeholders; all statistics have been reviewed and approved for use by the WSO Executive Committee as well as leaders from the Global Burden of Disease research group (WSO, 2022).

In 2020, there were 89.1 million stroke cases worldwide, 68.2 million ischemic stroke cases, 18.9 million intracerebral haemorrhages, and 8.1 million subarachnoid haemorrhages. Overall, Sub-Saharan Africa, some regions of the south-east United States, and East and South-east Asia had the highest age-standardised stroke prevalence rates in 2020. The age-standardised prevalence of ischemic stroke was highest in the eastern United States and sub-Saharan Africa (WSO, 2022). The highest age-standardised prevalence of intracerebral haemorrhage was found in Oceania, South-east Asia, and western sub-Saharan Africa. The age-standardised prevalence of subarachnoid haemorrhage was greatest in Japan. About 7.1 million fatalities globally in 2020 were directly related to cerebrovascular illness.

A total of 3.5 million people worldwide passed away from an ischemic stroke in 2020, 3.3 million from an intracerebral haemorrhage, and 0.4 million from a subarachnoid haemorrhage. The regions with the highest age-standardised stroke mortality in 2020 were Central, South-east, and East Asia; Oceania; and sub-Saharan Africa. Eastern Oceania had the highest age-standardised mortality attributable to ischemic stroke, followed by South-East (WSO, 2022). Asia, western, central, and eastern Sub-Saharan Africa, and then Oceania. The regions with the highest estimated age-standardised mortality from subarachnoid haemorrhage were Oceania, Andean Latin America, and Central Asia.

Global Burden of Stroke Risk Factors

High blood pressure (HBP)

Based on statistics from 2020, Central and South-east Asia, Eastern and Central Europe, and portions of Africa and the Middle East have the highest age-standardised mortality rates owing to high systolic blood pressure (SBP) (NCD Risk Factor Collaboration, 2021). The number of deaths associated with SBP 140 mm Hg increased in high-middle-income, middle-income, low-middle-income, and low-income countries between 1990 and 2015, but not in high-income countries (NCD Risk Factor Collaboration, 2021). According to 2015 data, there were 3.47 billion adults worldwide with a SBP of 110 to 115 mm Hg or above. Of this group, 874 million had SBP below 140 mm Hg (NCD Risk Factor Collaboration, 2021).

The prevalence of physical inactivity in 2016 was reported to be 27.5% of the population globally (World Health Organization, 2018). There were higher numbers of women than men reporting insufficient physical activity

globally (World Health Organization, 2018). In 2020, mortality rates attributable to low physical activity were highest in North Africa, the Middle East, and southern sub-Saharan Africa (World Health Organization, 2021).

According to data from 2020, the regions with the lowest age-standardised mortality rates attributable to high BMI were high-income Asia Pacific, Oceania, Central Asia, the Middle East and North Africa, southern sub-Saharan Africa, and locations in Central and Eastern Europe, central sub-Saharan Africa, and central Latin America. The regions with the highest rates were the Middle East and North Africa (NCD Risk Factor Collaboration, 2021). In 2020, about 2.40 million deaths worldwide were attributed to high BMI (NCD Risk Factor Collaboration, 2021).

According to data from 2020, diabetes affected 243.3 million men and 229.0 million women globally (International Diabetes Federation, 2020). The regions with the highest age-standardised mortality rates associated with high fasting plasma glucose were Oceania, sub-Saharan Africa, Central Latin America, and parts of South and Southeast Asia. Oceania, southern sub-Saharan Africa, central sub-Saharan Africa, and central Latin America had the highest age-standardised diabetes mortality rates (NCD Risk Factor Collaboration, 2021). The highest age-standardised prevalence of diabetes was found in North America with high incomes, followed by North Africa and the Middle East, the Caribbean, and Central Latin America (NCD Risk Factor Collaboration, 2021). The global economic impact of diabetes was $1.3 trillion in 2015. By 2030, it is projected to rise from $2.1 to $2.5 trillion (NCD Risk Factor Collaboration, 2021).

Stroke Dynamics in Ghana

Stroke is a cerebrovascular disease that damages the arteries and eventually causes brain damage and death (Agyeman *et al*., 2006; Sarfo, Acheampong, Oparebea, Akpalu, & Bedu-Addo, 2014). According to the WHO's (2015) report on strokes, middle-income nations had different patterns of strokes than high-income ones. Stroke is the fifth most common cause of death and disability. The CDC lists stroke as the fourth most common cause of disability and fatality in high-income countries outside the United States.

According to the World Health Organisation, between 1990 and 2010, stroke had a fatality rate of 26% in Ghana, making it the second-most lethal disease behind malaria (Baatiema *et al*., 2017). Ghana, one of the countries with middle-lower incomes, accounted for 87 percent of all stroke deaths (Donkor, Tetteh-Quarcoo, Nartey & Agyeman, 2012). According to these figures, high-income countries have a lower incidence of stroke than middle, and low-income nations. This might have happened because of comprehensive stroke preventive measures, such as population-level hypertension control and public education on stroke risk factors (Sarfo *et al*., 2014). As diabetes, malaria, and tuberculosis are lifestyle diseases that may have been avoided by raising public awareness of their risk factors, stroke has become a public health problem.

Due to the availability of high-quality, evidence-based care, the incidence of stroke and its related mortality rate are lower in high-income countries than in middle- and low-income countries (Baatiema *et al*., 2017). Stroke care in middle-income countries is characterised by a lack of knowledge and expertise among medical professionals and other carers,

according to Baatiema *et al*. (2017). The absence of stroke-specific medical equipment and the exorbitant expense of stroke therapy are further hallmarks of stroke care in middle-income nations (Baatiema *et al*., 2017). This can be explained by the high rates of stroke-related disability and death in most developing or low-income countries (Agyeman *et al*., 2006; Baatiema *et al*., 2017).

Stroke is the fourth most common cause of death in Ghana, according to 32 sentinel sites between 2012 and 2016 (Baatiema *et al*., 2017). Males aged 48 to 60 made up roughly 53.5% of the deaths, while females aged 41 to 52 made up the remaining 46.5% (Baatiema *et al*., 2017). Research suggests that people in their middle years, between 40 and 60, account for the majority of stroke cases. The figures provided here show the trend of stroke cases as reported in the inpatient units of all 32 institutions. According to Donkor, Tetteh-Quarcoo, Nartey & Agyeman (2012) from January 2006 to December 2007, the in-patient department at Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana, registered 1054 stroke cases. This number had a male-to-female ratio of 1.0:0.96, with 537 males and 513 females making up 51.1% and 48.9%, respectively, of the total. The male-reported cases have an average age of 60, and the female-reported cases have an average age of 65 (Baatiema *et al*., 2017).

At the same hospital, Sarfo *et al.* (2014) (i.e., KATH) found that of the 265 stroke patients identified in 2012, 150 (56.6%) were female and the remaining 115 (43.4%) were male, resulting in a female-to-male ratio of 1.3:1. In this study, the average age of the female stroke patients was 65 years old. However, the researcher's use of a sizable sample size of 1054 can be to blame

for the inconsistent findings. This is in contrast to Sarfo *et al.* (2014) small sample size of 265. In both investigations, it was found that hypertension is the major risk factor for stroke. However, Sarfo *et al*. (2014) found that, in contrast to men, more women with a history of obesity or who were already obese had hypertension. The social determinants of stroke should be taken into account in public health intervention strategies, even though Sarfo *et al*. (2017) found that obesity, hypertension, and physical inactivity are the three high-risk factors, with 85%, 73%, and 58% prevalence among the cohort, respectively. Moreover, Sarfo *et al.* (2014) discovered that socioeconomic class has an impact on recovery from a stroke if patients survive. Individual socioeconomic level differences have an impact on both short-term and long-term outcomes following a stroke (Sarfo *et al*., 2014).

Stroke Studies in Ghana

Although the impact of stroke on developing countries is largely significant, there has not been serious research on stroke in Ghana. Sampan-Donkor (2014) studied the awareness of stroke in Accra, Ghana. They conducted a cross-sectional study involving 63 households in each of the 11 sub-metropolitan areas of Accra. The questionnaires were used to collect data on stroke awareness from a randomly selected household. The study used logistic regression to identify the predictor (stroke risk factors, stroke warning signs, and organ affected) main outcome variables.

The results indicated that 40% of the 693 respondents confirmed the brain as the organ affected. Less than 50% could recognise any of the stroke risk factors or any of the stroke warning signs. More than 70% of the respondents could believe that stroke is a preventable disease or that stroke

requires emergency attention. The results also show that predictors of stroke awareness were age 50 or older, the presence of stroke risk factors, and Christian religion. The findings indicated that stroke is seen as a serious and preventable disease. Community-based education programmes on stroke awareness should be conducted to decrease the risk of stroke.

Donkor (2014) also conducted a longitudinal study among stroke outpatients and inpatients at the Korle-Bu Teaching Hospital in Ghana. This study aimed to investigate the epidemiology of bacteria among stroke patients at the Korle-Bu Teaching Hospital, involving 55 outpatients and 16 inpatients selected from the hospital's physiotherapy and stroke admission ward. Patients were followed up weekly for six months. Each patient's urine sample was analysed weekly.

Demographic statistics about patients were extracted from clinical records. New cases of bacteriuria were recorded from each group type (outpatient and inpatient). In his finding, he indicated that the prevention of bacteriuria among stroke inpatients and outpatients was 18.8% (3/16) and 10.9% (11%), respectively. There was one new case of bacteriuria in each group. On average, there were about 1/9 (11%) of bacteriuria cases among patients. Pyuria and severe stroke were identified as predictors of bacteriuria, and Escherichia coli was the most common. Common organism implicated in bacteriuria and was susceptible to amikacin but restricted to Augmentin, ampicillin, cefuroxime, cotrimoxazole, meropenem, norfloxacin, and tetracycline. Overall, bacteriuria is a common complication among stroke patients at KBTH. Stroke severity appears to be the main stroke-related determinant of bacteriuria among stroke patients.

Agyeman *et al*. (2006) studied time to admission for acute stroke and transient ischemic attack. The purpose of this research was to investigate the effect of thrombolysis depending on the time from stroke onset to treatment time and from symptom onset to admission (TTA) to the stroke unit. Medical records of patients were extracted from the neurological department. This included 615 consecutive strokes or transient ischemic attacks admitted to the unit within 48 hours after the index stroke. Results from this study revealed that the median TTA was 180 minutes. Referral by emergency medical services, stroke in the carotid territory, and the Institute of Health stroke scale were associated with shorter pre-hospital delays. The results also indicated that adjusted time for travel hours (adj. TTA) and all the other variables were still statistically significantly associated with time to admission.

Regression analysis was also conducted, and the results confirmed the previous independent association between referral by EMS, high NIHSS scores, and the first-ever cerebrovascular event with a shorter adj TTA. The study concluded that factors such as the location of a stroke patient and NIHSS scores influence the time to admission. Another study that studied stroke in Ghana is Baatiemal *et al*. (2017). The main aim of their study was to identify and evaluate acute stroke services in Ghana as compared with global best practises. A hospital-based survey was conducted. Samples included are from 11 major referral hospitals from November 2015 to April 2016. A pretest, structured questionnaire was used to collect the data available for hospital-based acute stroke. The respondents included neurologists, physician specialists, and medical officers. Among the 11 medical units sampled, the results were varied. The outcome showed one teaching hospital had a stroke

unit; however, thrombolytic therapy using recombinant tissue plasminogen activator for acute ischemic stroke was available in any of the study hospitals.

Aspirin therapy was common among the 11 study units. Six out of eight study centres reputed to have a brain computed tomography (CT) scan were functional during the study period. For 36.4% of hospitals, functional magnetic resonance imaging (MRI) scans were also available. Acute stroke care by a specialist was found in 36.4% (4) of the study hospitals, while none of the study hospitals had a speech pathologist to support the provision of acute stroke care. The findings from this study show that there is limited and variable provision of evidence-based stroke services and a low priority for stroke care.

Predictors of Stroke Severity

Stroke is one of the leading causes of morbidity and mortality worldwide and the leading cause of disability (Rost *et al.*, 2016). Although secondary preventive measures are on the rise, patients still face different time points after stroke (Williams, Yilmaz, & Lopez-Yunez, 2000). The ability for a patient to recover from a stroke depends on its severity and how quickly the patient gets medical attention. Several scales are used in determining the functional independence of the survivors. These scales (the Modified Rankin Scale (mRS), Canadian Neurological Scale (CNS), Barthel Index (BI), National Institute of Health Scale (NIHSS), and many others) are used in determining the severity of stroke, which may be grouped into three categories: mild, moderate, and severe.

Jones *et al.* (2000) studied racial variations in initial stroke severity. That was to determine whether there is a racial difference in initial stroke

severity between blacks and whites (Jones *et al.*, 2000). Secondary data were obtained from nine (9) nationwide cohort studies involving 1073 participants with acute stroke. The initial stroke severity of each patient was determined using the Canadian Neurological Scale (CNS), which categorises stroke severity scores as mild (8.5 to 11.5), moderate (6.0 to 8.0), and severe (0.0 to 5.5) for each race. Participants were clinically followed up within the Veteran Health Administration (VHA), located across the United States, between April 1, 1995, and March 31, 1997. Multivariate linear model analysis was performed using initial stroke severity as the response variable, while covariates such as age, race, atrial fibrillation, diabetes mellitus, smoking, stroke type, prior stroke, prior nursing at home, and hypertension were used as the explanatory variables.

The results indicated that blacks and whites differed in several characteristics: blacks had higher initial stroke severity compared to whites (mean CNS score of 7.96 against 8.32) at a 0.5-point difference on the scale using analysis. In this study, they found out that some factors could have affected the racial variation. This study utilised prospective studies and monitored participants over a period of time. The results obtained from multivariate linear regression were very clear. The exclusion of female covariates from the analysis may make a significant difference in the outcome. The result did not also indicate what happened within the time points over the period of time.

According to Chen *et al*. (2019), smoking is a well-established risk factor for stroke, and smoking cessation has been suggested for stroke prevention. Patients with their first-ever stroke were enrolled and followed in

the NSRP (Nanjing Stroke Registry Programme). Smoking status was assessed at baseline and reassessed at the first follow-up. The primary end point was defined as a fatal or nonfatal recurrent stroke after 3 months of the index stroke. The association between smoking and the risk of stroke recurrence was analysed with a multivariate Cox regression model.

At baseline, among the 3069 patients included, 1331 were non-smokers, 263 were former smokers, and 1475 were current smokers. At the first follow-up, 908 patients quit smoking. After a mean follow-up of 2.41 years, 293 patients had a stroke recurrence. With non-smokers as the reference, the adjusted hazard ratios for stroke recurrence were 1.16 in former smokers, 1.31 in quitters, and 1.93 in persistent smokers. Among persistent smokers, hazard ratios for stroke recurrence ranged from 1.68 in those who smoked 1 to 20 cigarettes daily to 2.72 in those who smoked more than 40 cigarettes daily.

Unadjusted hazard ratios (HRs) for stroke recurrence in the study compared with nonsmokers were 1.26 (95% CI, 0.82-1.93) in former smokers, 1.20 (95% CI, 0.90-1.60) in quitters, and significantly higher in persistent smokers. Persistent smokers continued to have a greater risk of having a stroke (HR, 1.93; 95% CI, 1.43-2.61) compared to nonsmokers, even after controlling for key variables. Similar findings were made regarding the link between cigarette smoking and the risk of ischemic stroke that recurs. After adjusting for the previously mentioned factors, quitting smoking was independently linked to a lower risk of stroke recurrence and ischemic stroke recurrence. A proper design was appropriately used in this study. Patients records were retrieved from a medical facility for a period of three years. The

results did not include hazard ratios of the covariates in different disease states.

Rist *et al.* (2010) studies on alcohol consumption indicated that the relationship between alcohol consumption and functional outcomes from stroke is sparse. The study used a prospective cohort study with 21,862 men who participated in the Doctors' Health Survey, gave baseline data on alcohol intake, and had no history of stroke or transient ischemic attack (TIA). Five types of alcohol consumption were established; outcomes included TIA, modified Rankin Scale (mRS) = 0–1, MRS = 2–3, and mRS = 4–6. The researchers used multinomial logistic regression to evaluate the relationship between levels of alcohol consumption and functional outcomes from stroke.

Results from the study show that during a mean of 21.6 years of follow-up, 767 TIAs and 1393 strokes (1157 ischemic, 222 hemorrhagic, and 14 unknown types) occurred. Men who consumed one drink per week had the lowest associated odds for any outcome. Compared with men who did not experience a TIA or stroke and who consumed This study did not show a strong relationship between alcohol consumption and functional outcomes after stroke. They could not also establish a relationship between alcohol intake and stroke severity within the various time points.

A major public health concern in Ghana is stroke recovery, according to Amuah (2019), because of the high mortality and morbidity rates connected to strokes. Using a quantitative study, she examined the important influence that income has on the onset of stroke. Particularly in middle-income nations like Ghana, her research on how money affects stroke recovery is less well recognised and appreciated. The goal of the phenomenological study was to

offer in-depth insight into any potential relationships between Ghanaian families' income and stroke recovery. The study used research questions as a guide to discover how stroke survivors in Ghana felt about the financial and environmental hazards related to stroke recovery. A purposive sampling strategy was used to interview 15 stroke survivors. Data was coded using the Nvivo software and then thematically evaluated. The findings showed that stroke patients' housing choices are influenced by their income, increasing their exposure to environmental risk and delaying their recovery from stroke.

Also, the capacity of stroke patients to obtain healthcare services, including receiving medical treatment, purchasing recommended medications, and having access to physiotherapy, was influenced by their socioeconomic level. By using the knowledge gained from this study to influence policy changes in healthcare delivery systems, positive social change may be facilitated. Hence, include income-generating techniques and environmental risk problems in intervention programmes for stroke recovery.

In 2016, Rost *et al*. (2016) conducted a prospective analysis on outcome predictors of stroke severity for four countries. The authors aimed to implement an international pilot project to validate mRS and NIHSS scores as reliable predictors of outcomes for future use. Out of 1034 admitted patients for acute stroke, 614 of them had a set of NIHSS and both mRS values recorded. Five hundred and seven (507) patients could be linked to administrative data (Rost *et al*., 2016). Patients were followed up at 30 and 90 days after the index stroke between March 1, 2012, and April 30, 2012. Logistic regression models were fitted with severity categories using NIHSS scores (0 to 6 mild; 7–16 moderate; and 17–40 severe) as the dependent

variable. Age, sex, and the comorbidity index (CMI) were used as independent variables.

The results revealed that stroke severity was similar between country groups at the hospital. The proportion of variation that was explained was 70% to 40% for the CMI and 11.3 to 25.1 for the NIHSS score, the highest agreement between the 30–90-day mRS score (weight) (Jones *et al.,* 2000). In this study, the authors identified that mRS is accepted worldwide as a measurement of post-stroke outcome and as a 90-day measurement of mRS. Unfortunately, they did not cover the proportion of variation among the various disease states.

Habibi-Koolaee *et al.* (2018) prospectively studied the prevalence of stroke risk factors and their distribution based on stroke subtypes in Gorgan between 2015 and 2016. This research aimed to assess stroke subtype and major risk factors in patients admitted to Sayad Shirazi Hospital. Data were retrieved from the medical records. Patients were identified using magnetic resonance imaging (MRI) or computed tomography (CT) scans after consulting the neurologist or physician. The relationship between risk factors (age, gender, ethnicity, and area of residence) and stroke subtype was modelled using logistic regression, and the 0.05 chi-square level of significance was set.

The result has shown that out of 375 cases, two-thirds were marked with ischemic stroke, with a mean age of 66.4 years and a standard deviation of 14.2 for men and 64.6 years and a standard deviation of 14.2 for women. There exists a significant difference between stroke subtype and age group and hospital outcome. The multiple logistic regressions indicated that hypertension

and dyslipidemia significantly increase the risk of ischemic stroke (Habibi-Koolaee *et al*., 2018). However, the reduced model affirmed that only comorbidity risk factors such as hypertension, diabetes, and dyslipidemia significantly affect stroke severity.

However, determining the characteristics of patients with their first-ever ischemic stroke and identifying predictors and long-term mortality of stroke severity were studied between 2004 and 2008 using patients' medical records (Corso *et al*., 2014). Multivariate logistic regression models, Kaplan-Meier estimates, Cox, and proportional hazards models were used to determine predictors. Covariates were comorbidity risk factors (hypertension, demographic factors, diabetes mellitus, therapy at admission, and pathophysiology), which were used as explanatory variables, while stroke severity was the response variable.

Predictors of stroke severity at admission were very old age (odds ratio 2.98, 95% confidence interval [CI] 1.75–5.06), female gender (OR 1.73, 95% CI 1.21–2.40), atrial fibrillation (OR 2.76, 95% CI 1.72–4.44), low ejection fraction (OR 2.22, CI 95% 1.13–4.32), and cardioembolism (OR 2.0, 95% CI 1.36–2.93). Predictors of long-term mortality were very old age (hazard ratio [HR] 2.02, 95% CI 1.65–2.47), prestroke modified Rankin scale 3–5 (HR 1.82; 95% CI 1.46–2.26), Charlson Index 2 (HR 1.97; 95% CI 1.62–2.42), atrial fibrillation (HR 1.43, 95% CI 1.04–1.98), and stroke severity (HR 3.54, 95% CI 2.87–4.36).

In predicting long-term outcomes after stroke, Ziegler *et al*. (2008) predicted functional recovery and survival versus death using BI and NIHSS scores from the VISTA data set (www.vista.gla.ac.uk). The results revealed

that 4441 patients' BI was recorded after 90 days and that 1979 had recovered while 2471 had not functionally recovered (Ziegler *et al*., 2008). The final model was able to correctly classify patients at 70.4% survival and 72.9% functional recovery (Ziegler *et al.*, 2008). Because the prediction was slightly pessimistic for patients in the controlled trials, adapting the intercept improved the accuracy to 74.8% survival and 74.0% functional recovery (Ziegler *et al.*, 2008). In predicting three-month mortality among patients hospitalised for their first-ever acute ischemic stroke, Chang *et al*. (2006) investigated factors related to 3-month mortality at admission in patients with their first-ever acute ischemic stroke at a Taiwan medical centre within 48 hours after the index event.

Analysis was done using multivariate logistic regression to identify the major predictors of acute stroke three months after the index event. The National Institutes of Health Stroke Scale (NIHSS) score was used as a measure for stroke severity. The stroke subtype was classified into anterior circulation and posterior circulation to investigate the potential association of posterior circulation ischemic stroke with high mortality. Among the 360 patients enrolled, the in-hospital mortality rate was 7.8% (28 deaths), and the 3-month mortality rate was 9.7% (35 deaths). Twenty-seven deaths (77%) were stroke-related (Chang *et al*., 2006). Risk factors for mortality at 3 months included sex (OR, 3.18; 95% confidence interval [CI], 1.08–9.41; NIHSS) at admission (per unit increase: OR, 1.17; 95% CI, 1.12–1.22; P 0.001), history of cardiac disease (OR, 2.73; 95% CI, 1.04–7.16; P = 0.042), and posterior circulation stroke (OR, 5.25; 95% CI, 1.92–14.36; P = 0.001) (Chang *et al*., 2006).

Long-term predictors of activity limitation and stroke outcomes were investigated (Gadidi, Carmeli, & Bornstein, 2011). That was to determine factors at the index stroke and predict the level of activity participation and limitation. One hundred and thirty-nine (139) participants admitted at the Sheba Medical Centre in Israel were prospectively followed up for four years. The Barthel Index (BI) (activity limitation; BI 95) and the Frenchay Activities Index (FAI) (participation restriction; FAI 30) were the outcome measures. The perception of recovery was assessed using two simple questions. At the end of the four years, nine patients (6.4%) were lost to follow-up, 71 (54.1%) participants had survived, 42.3% had activity limitation, 28.2% were classified as restricted in participation, and 78.1% thought that they were not fully recovered (Gadidi, Carmeli, & Bornstein, 2011). Age at index stroke and disability in the acute phase significantly predict activity limitation. No demographic variable or baseline clinical feature predicted participation restrictions. A positive association was noted between activity limitation and participation restriction four years post-stroke (Gadidi, Carmeli, & Bornstein, 2011).

Baseline NIHSS for stroke severity is a strong predictor of stroke outcome (Lemmens, 2018). Lemmens (2018) predicted outcomes in acute stroke based on baseline severity and improvement in the first twenty-four (24) hours after the index event. The author hypothesised that the change in NIHSS in the first 24 hours after stroke improved stroke outcome prediction. Records for three hundred and sixty-nine patients were retrieved from the Leuven Genetic Study. NIHSS scores were calculated over 90 days of

admission. Multiple logistic regression models were used to independently predict outcome measures.

The results revealed that NIHSS was associated with functional outcomes. The multivariate model significantly predicted age and NIHSS scores [the area under the curve improved by including the delta NIHSS (Lemmens, 2018)]. With one hundred and thirty-one (131) participants with moderate-to-severe stroke, the predictive model was more accurate when adding the NIHSS to the model, which included the NIHSS, age, and ischemic heart disease. In conclusion, the NIHSS is a predictor of stroke outcome.

A review of all eight articles on stroke severity identified age as a risk factor for stroke severity. Comorbidity risk factors (diabetes mellitus, hypertension) significantly affect stroke severity in all short- and long-term cohort studies. Some studies also identify the female gender as a risk in all the multivariate logistical models. Other factors such as atrial fibrillation, low ejection fraction, and cardioembolism also affect stroke severity among patients with an initial stroke.

Comorbidity and Rehabilitation of Stroke

Comorbidity: this means two or more disorders or illnesses are occuring in the individual at the same time or one after the other. Comorbidity may also describe interactions between the illness and the disease (National Institute on Drug Abuse, 2018). The impact of comorbidity on stroke survival remains unknown (Simić-Panić *et al*., 2018).

Simić-Panić *et al*. (2018) prospectively examined the effect of comorbidities in patients with ischemic stroke. They used the River Mead Mobility Index for mobility, the Barthel Index for independence in ADL, and

the mRS for total disability. The effect of comorbidities on stroke functional recovery was studied in Taiwan. Chronic pulmonary disease and a prior history of hemiplegia were the two most detrimental diseases, according to analysis of the effects of the various comorbidities on stroke patients' daily living activities.The study showed that comorbidities, chronic pulmonary disease, and hemiplegia can affect functional recovery (Jenei, Nagy, Kovacs, & Horvath, 2018).

A follow-up FIM score may be best explained by the FIM at admission and the contribution of the weighted comorbidity index to functional outcome, according to Karatepe, Gunaydin, Kaya, and Turkmen, (2008). Using the Liu Comorbidity Index, comorbidities were evaluated. Using the Functional Independence Measure, functional independence was assessed (FIM). Investigations were done into the connection between comorbidities and functional results. Using multiple stepwise regression analysis, the effect of comorbidities on the functional result was investigated. Comorbid disorders are widespread among stroke patients, according to this study's findings. They had a demonstrated negative link with functional outcomes; however, it was unclear what effect they had on functional outcomes.

Nelson *et al*. (2017) conducted a systematic scoping review of the evidence for stroke rehabilitation and comorbidity.The terms "stroke" and "rehabilitation" were combined to search an electronic database. Inpatient rehabilitation studies were included in the selection criteria. Randomised controlled trials (RCTs) were abstracted, and methods were changed to accommodate the volume of literature. The outcomes showed that 10771 distinct articles were found in the database search, and 428 RCTs that passed

screening were included. Patients with concomitant conditions were specifically included in three investigations. Fifteen percent (15%) of the articles lacked a list of additional conditions that were not included. The condition that was most frequently excluded was impaired cognition. 37% of articles said patients with a history of stroke were not included. Patients with one or more Charlson Index conditions were excluded in 24% of cases, while patients with at least one other medical condition were excluded in 83% of cases. This study made an initial attempt to map the literature on stroke rehabilitation and co-morbidity and identify research needs. Individuals with comorbidities were frequently left out of the existing research on stroke rehabilitation.

Berlowitz, Hoenig, Cowper, Duncan, & Vogel. (2008) used the Charlson Index, adjusted clinical groups (ACGs), and diagnosis cost groups (DCGs) to examine the influence of comorbidities in predicting stroke rehabilitation outcomes and to examine differences among three (3) commonly used comorbidity measures in how well they predict these outcomes. Research conducted by Berlowitz, Hoenig, Cowper, Duncan, & Vogel (2008) has shown that a total of 2402 patients were part of the Integrated Stroke Outcomes Database and started receiving stroke therapy at a VA facility in 2001. Three outcomes were assessed: change in FIM score, 6-month rehospitalization, and 6-month death. 8.6% of patients passed away, and 27.6% required rehospitalization during the 6-month follow-up period. During rehabilitation, the mean FIM score increased by an average of 20 points. Based on changes in statistics for logistic models and values for linear regression models, adding comorbidities to the age and sex models enhanced

their ability to predict these outcomes. The best models, based on DCGs, had a change of 0.111 in the FIM score and statistics of 0.74 for 6-month mortality and 0.63 for 6-month rehospitalization, while ACG and DCG models fared equally. According to the studies, comorbidities play a significant role in predicting the success of stroke therapy. Models that could be used to evaluate the quality of care have substantial consequences for how they are classified.

Length of Stay on Rehabilitation

A retrospective observational cohort study was conducted by Cegarra and Opisso (2020) with 172 impatients admitted to a rehabilitation facility between 2007 and 2019. The study's objectives were to determine factors that would predict length of stay (LOS) in a sample of patients who were primarily severe cases and to examine how socioeconomic status would have affected functionality upon admission. Bonferroni correction revealed a significant ($p = 0.0002$) correlation between associations and stroke length of stay. Nine different multiple linear regression models were run with the variables. 36.63% were intermediate, 63.37% were severe, and no mild subjects were considered. Total functional independent measure (FIM) and hemiparesis were the most important LOS determinants, followed by cognitive FIM and severity, home accessibility ($p = 0.043$), and hemiparesis (adjusted).

In their dataset, known LOS predictors (such as depression and ataxia) across all stroke severities were not shown to be statistically significant. A weak correlation between socioeconomic status and overall FIM was discovered. The patients' respective median total FIM at admission was 61.5, 50, or 41 when their socioeconomic situation was stratified into mild, important, and severe social risk groups. There were significant differences

between the mild and important groups and between the mild and severe groups as well. The study also showed that a few variables (National Institutes of Health Stroke Scale, FIM, and home accessibility) identified in their literature as significant predictors of LOS within the stroke population were also significant in their dataset, explaining less than 25% of the LOS variance. Most of the 30 known predictors examined (such as depression, age, recurrent stroke, ataxia, orientation, verbal communication, etc.) were not significant, indicating that factors other than functional, socioeconomic, medical, and demographic variables excluded from this study (such as the intensity of rehabilitation sessions) have significant effects on LOS for severe patients.

Qureshi, Ullah, Jenkins, & Janjua (2018) performed a retrospective cohort study on 60 stroke patients who were discharged from an inpatient stroke rehabilitation unit in order to examine the variables associated with the length of inpatient stay of stroke patients at a tertiary care facility. Individuals who were discharged against medical advice or died before completing their rehabilitation were not included in the study. The study excluded patients who were difficult to discharge or who had to be transferred to another medical facility due to medical instability.

According to research findings, there were 60 patients, 62% of whom were men and 38% were women. Age, length of stay in acute care (LOSa), length of stay in rehabilitation (LOSr), functional status at admission (FIMa), and functional status at discharge (FIMd) all have mean descriptive analyses that are, respectively, 63.4 years, 22.1 days, 48.8 days, 59.7 days, and 80.8 days. Those who had hemorrhagic strokes had higher LOS. FIMd shows a high negative association with age and LOSa and a substantial positive

correlation with FIMa. Age and FIMa have a negative connection with LOSr. The sole significant variable in a multivariate linear regression model was age. The study came to the conclusion that earlier rehabilitation therapies during acute stroke care should be prioritised since they can improve patient functional outcomes during inpatient rehabilitation and reduce the amount of time spent in the rehabilitation unit.

After completing a stroke rehabilitation programme in Hong Kong, Ling (2004) conducted research to find markers that predict the length of hospital stay (LOS), increase in the Functional Independence Measure (FIM), and discharge placement. 1,111 stroke patients who were hospitalised at Kowloon Hospital between April 1, 2000, and March 31, 2002, were retrospectively evaluated by the researcher. Age, gender, marital status, pre- and post-hospital living situation, side of impairment, and functional status as measured by FIM subtotal scores for admission and discharge in the areas of self-care, sphincter control, transfer, mobility, communication, and social cognition were all gathered. The LOS, FIM gain, and discharge placement were used to gauge the outcome.

The study's findings indicate that age, FIM gain, arrival FIM subtotal scores for mobility, transfer, communication, self-care, and pre-hospital institutional living are all highly significant direct predictors of rehabilitation length of stay (LOS). The mean FIM score improvements were 19.8 points (ranging from –10 to 69; SD, 12.5). Age, gender, marital status, prehospital living alone versus prehospital living with family, prehospital living in an institution versus prehospital living with family, and the admission FIM sub-

total score in locomotion, self-care, and social cognition were all significant predictors of discharge placement.

In conclusion, the study identified factors that could predict how stroke rehabilitation patients in Hong Kong would do after being discharged. Occupational therapists, who are experts in functional evaluation and training, can begin a suitable treatment plan early to promote safe discharge and work with doctors to choose suitable resettlement plans for their patients following discharge. This study estimated the length of stay of stroke patients in the health facility until discharge from the unit for rehabilitation to be continued at the patient's home. The study did not estimate the length of recovery from stroke. The research could not also inform us about the severity from the time of admission until discharge.

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Criticism and Gaps Identified in Review Articles

In medical research, the development of diseases occurs over time. The above articles concentrated on forecasting the risk factors for stroke severity based on different designs and modelling concepts.

Jones *et al.* (2000), Rost *et al.* (2016), and Lemmens (2018) used the initial count on stroke severity in predicting the risk factors of stroke: age,

female gender, and stroke type significantly predicted early recovery, while comorbidity factors increased severity. The effects of these covariates at a single time point are known. These researchers failed to estimate these effects of the covariate as the diseases progressed. According to Caruana *et al*. (2015), a longitudinal study is used in studying the relationship between risk factors and the development of diseases. The above studies undertook a cross-sectional study. These may employ multiple variables at a given time. But they provide no information concerning the influence of time on the variables they measured.

Chang *et al*. (2006), Gadidi, Carmeli &Bornstein (2011), Corso *et al*. (2014), Habibilaee *et al*. (2018), and Ziegler *et al.* (2008) all predicted outcome measures of stroke using a longitudinal approach. Chang *et al*. (2006),) conducted 3-month longitudinal studies on acute stroke recovery, while Gadidi, Carmeli, and Bornstein (2011) did 4-year prospective studies. They assessed stroke severity at the end of the four years. Questions were answered by stroke survivors and by proxy for non-survivors. The Barthel index was used to measure the activities of daily living of survivors. The outcome measures were severity and death at the end of the four years.

In Chang *et al*. (2006), the study should have a clear research question that defines the purpose of the study. The study provided a well-defined study population, including the inclusion and exclusion criteria. A sample size of 360 was a representative of the population. The study have a clear description of the data collection methods, including the variables used. The variables clearly defined and include demographic, clinical, and laboratory data.

Gadidi, Carmeli & Bornstein (2011), examines the predictors of activity limitation and participation restriction in stroke survivors in the long-term. The authors conducted a systematic review of studies that followed stroke survivors for at least 6 months after stroke onset. They found that factors such as age, gender, stroke severity, and comorbidities were consistently associated with poor long-term outcomes. Additionally, cognitive and emotional factors, such as depression and executive function, were also found to be important predictors. The authors suggest that these factors should be taken into consideration when designing interventions to improve activity limitation and participation restriction in stroke survivors. This article did not indicate the proportion of the covariate effect. Also, the articles lack an overall critical analysis of the studies. For example, they do not discuss the limitations of the studies or the generalizability of their findings. Additionally, there is no discussion on the quality of the research design or data collection methods used in the studies.

The articles could benefit from a clearer and more structured presentation of the findings. The summary of each study's results could be more concise and focused on the most relevant findings. Additionally, there could be a more explicit discussion of how the findings of each study contribute to our understanding of stroke in Ghana.

The articles could also benefit from a more comprehensive and up-to-date review of the literature on stroke in Ghana. While the four studies summarised in the articles provide valuable insights, there may be other relevant studies that have been published since their publication. Therefore, it

would be helpful to provide a more complete overview of the current state of research on stroke in Ghana.

The articles also provided a useful starting point for those interested in learning about stroke in Ghana. However, there is room for improvement in terms of providing a more critical analysis of the studies, a clearer presentation of the findings, and a more comprehensive review of the literature.

The statement that the impact of comorbidity on stroke survival remains unknown is correct, based on the Simi-Pani *et al*. (2018) study cited. The study accurately summarises the methodology and findings of this study, which investigated the effect of comorbidities on stroke functional recovery in patients with ischemic stroke in Taiwan. The statement that chronic pulmonary disease and hemiplegia can affect functional recovery is also accurate based on the study's results.

The summary of Karatepe *et al.* (2008) study on the effect of comorbidities on functional outcome in stroke patients is also accurate. The study used the Liu Comorbidity Index to evaluate comorbidities and the Functional Independence Measure to assess functional independence. The study's findings suggest that comorbid disorders are prevalent among stroke patients and have a negative impact on functional outcome.

Nelson *et al. (2017*) scoping review of stroke rehabilitation and comorbidity is also accurate. The study searched an electronic database for articles on stroke rehabilitation and included inpatient rehabilitation studies in its selection criteria. The review found that individuals with comorbidities were frequently excluded from stroke rehabilitation research, highlighting a gap in the literature.

Also, the review provided an accurate summary of Berlowitz *et al.* (2008) study on the influence of comorbidities in predicting stroke rehabilitation outcomes. The study used the Charlson Index, adjusted clinical groups (ACGs), and diagnosis cost groups (DCGs) to examine the impact of comorbidities on change in FIM score, 6-month rehospitalization, and 6-month death. The study's findings suggest that comorbidities play a significant role in predicting the success of stroke therapy and that models that could be used to evaluate the quality of care have significant consequences for how they are classified.

However, none of these articles reviewed estimated the possible probabilities of transiting from one disease state to another.

How to Fill the Gaps

A stroke patient on rehabilitation has undergone a series of stages; mild, moderate, severe, and absorbing state. The transition between the states depends on how the patient adhered to treatment. Multi-state models would be used to describe how the individual patients move between a series of states in continuous time. An individual in the state i at time t will move to a less or more severe state at the time $t+1$ depends on whether the patient adheres to treatment. We would retrospectively extract two-year data from TTH, where stroke patients have been monitored at two-month intervals by the medical unit. We would focus on fitting a multi-state model to continuously observe the recovery process, where the state of each individual is known at all times in the study period. A patient can advance or recover from the consecutive state while alive or die at any stage. The various transition probabilities would be extracted using a transition intensity matrix of

$$q = \begin{bmatrix} q_{11} & q_{12} & q_{13} & q_{14} & q_{15} \\ q_{21} & q_{22} & q_{23} & q_{24} & q_{25} \\ q_{31} & q_{32} & q_{33} & q_{34} & q_{35} \\ q_{41} & q_{42} & q_{43} & q_{44} & q_{45} \end{bmatrix}$$

Our research will also include a model that will estimate the effect of each covariate in the various states. The effect of a vector of the explanatory variables $\boldsymbol{Z_{ij}}$ on the transition intensity for the individual at the time will be modeled using the proportional intensity:

$$q_{rs} = q_{rs}^{0} \exp\left(\beta_{rs}^{T} \boldsymbol{Z_{ij}}\right)$$

Where q_{rs}^{0} is the relatively uninformative baseline intensities and β_{rs} is the log hazard ratio. The likelihood will then be maximized over q_{rs}^{0} and β_{rs} (Jackson, 2011). The total length of stay at each state will also be estimated; the average period in a single stay in a particular state.

Data Used and Methodology

In all the eight articles reviewed, Jones *et al*. (2000), Rost *et al*. (2016), Habibi, Shahmoradi, Kalhori, Ghannadan, and Younesi (2018) did follow-up studies to extract secondary data from medical records to predict risk factors that significantly influence early stroke recovery. Jones *et al*. (2000) studied racial variation in initial stroke severity. That was to determine whether there is a racial difference in initial stroke severity between blacks and whites. Secondary data were obtained from nine (9) sites nationwide cohort studies of 1073 participants with acute stroke. Rost *et al*. (2016) also conducted a prospective analysis on outcome predictors of stroke severity for four countries. Patients on rehabilitation were followed at 30 and 90 days after index stroke between March 1, 2012, and April 30, 2012. Habibi-Koolaee *et*

al. (2018), prospectively studied the prevalence of stroke risk factors and their distribution based on stroke subtypes in Gorgan between 2015 and 2016. This research aimed to assess stroke subtype and risk factors in patients admitted to Sayad Shirazi Hospital. They identified Patients using magnetic resonance imaging or computed tomography (CT) scan.

Gadidi, Carmeli, & Bornstein (2011) determined factors at index stroke and predicted the level of activity participation and limitation. This research is a prospective cohort study, which included all patients hospitalized with an acute first ischemic or hemorrhagic (not including transient ischemic attacks) treated at Sheba Medical Center between February and March 2004 as part of the National Acute Stroke Israeli Study. A comprehensive form for data collection was designed containing detailed demographic characteristics. Stroke severity was determined according to the National Institutes of Health Stroke Scale (NIHSS) guidelines. The Barthel Index (BI) (activity limitation; BI<95) and Frenchay Activities Index (FAI) (participation restriction; FAI<30) were the outcome measures. These were estimated after subjects survived up in the fourth year. Questionnaires were used for data collection. Patients that survived after being censored responded to the questions via telephone call at their respective homes. Non-survivors responded by proxy.

Chang *et al*. (2006) predicted three-month mortality among patients hospitalized for first-ever acute ischemic stroke, investigated factors related to 3 months mortality at admission in patients with first-ever acute ischemic stroke at Taiwan medical center within 48 hours after the index event.. A hospital-based laboratory with a movement testing system including position and torque sensors, Hemiparetic stroke survivors ($N = 20$) with upper-

extremity impairment recruited within 4 weeks post-stroke. The main outcome measures were: Kinematic parameters, including active range of motion, peak velocity, peak acceleration, movement smoothness, and movement speed; kinetic parameters, including isometric voluntary contraction of elbow extensors and flexors; and clinical measurement of motor impairment (FMA). Motor impairment was assessed using the Fugl-Meyer Assessment (FMA) of the upper extremity. The patient's angular elbow movement trajectory and its derivatives were recorded. Limb kinetics was quantified using maximum voluntary contractions. Subjects were examined at 1, 2, 3, 6, and 12 visit after stroke. The growth mixture model was used to characterize the recovery of patterns of the FMA over a year, and a logistic regression analysis was used to predict these patterns with the kinematic and kinetic measures recorded at one month.

In the recent study, we will use retrospective design to extract two-year secondary data from TTH where stroke patients are monitored at two-monthly intervals by the medical unit. One main objective of the research is to determine factors that influence stroke severity at the various transition states. The Barthel index was used to categorized stroke as No stroke (BI=20, state 1), mild stroke (BI<19, state 2), moderate stroke (BI<15, state 3), severe (BI<10, state 4), and absorbing state (death, state 5). Different measurement scales were used by the above researchers in measuring the severity of stroke including BI. We employed retrospective design in our data collection as well as Jones *et al.* (2000) and Chang *et al*. (2016) did. Meanwhile, Gadidi, Carmeli, and Bornstein, (2011), Mirbagheri & Rymer (2008). Rost *et al*. (2016) and Habibi-koolaee *et al*. (2018) kinds of research were based on

prospective design. All other reviewed works used multiple logistic regressions in estimating risk factors of stroke. We have adopted multi-state modeling techniques to estimate the hazard rates of transitions between two states. We will also embed the regression model into our CTMC in estimating the effect of each covariate.

Conceptual Framework

Longitudinal Study

A longitudinal study refers to an investigation where participant outcomes and possibly treatments or exposures are collected at multiple follow-up times. A longitudinal study generally yields multiple or repeated measurements on each subject. For example, stroke patients may be followed over time and monthly measures such as stroke severity may be taken over time. Such repeated measures data are correlated within subjects and thus require special statistical techniques for valid analysis and inference. A second important outcome that is commonly measured in a longitudinal study is the time until a key clinical event such as disease recurrence or death. Longitudinal studies play a key role in epidemiology, clinical research, and therapeutic evaluation. Longitudinal studies are used to characterize normal growth and aging, to assess the effect of risk factors on human health, and to evaluate the effectiveness of treatments.

In a prospective study participants can have their exposure status recorded at multiple follow-up visits. This can alleviate recall bias where subjects who subsequently experience disease are more likely to recall their exposure (a form of measurement error). In addition, the temporal order of exposures and outcomes is observed. A key strength of a longitudinal study is

the ability to measure changes in outcomes and or exposure at the individual level. Longitudinal studies provide the opportunity to observe individual patterns of change. When studying changes over time, there are many time scales to consider. In a cross-sectional study the comparison of subgroups of different ages combines the effects of aging and the effects of different cohorts. That is, comparison of outcomes measured in 2003 among 58-year-old subjects and among 40-year-old subjects reflects both the fact that the groups differ by 18 years (aging) and the fact that the subjects were born in different eras.

A retrospective study looks backwards and examines exposures to suspected risk or protection factors in relation to an outcome that is established at the start of the study. Many valuable case-control studies, such as Lane and Claypon's 1926 investigation of risk factors for breast cancer, were retrospective investigations. Most sources of error due to confounding and bias are more common in retrospective studies than in prospective studies. For this reason, retrospective investigations are often criticized. If the outcome of interest is uncommon, however, the size of prospective investigation required to estimate relative risk is often too large to be feasible. In retrospective studies the odds ratio provides an estimate of relative risk. You should take special care to avoid sources of bias and confounding in retrospective studies. The advantages of retrospective cohort studies are that they are less costly to perform than cohort studies and they can be performed immediately because they are retrospective. Also due to this latter aspect, their limitation is: poor control over the exposure factor, covariates, and potential confounders.

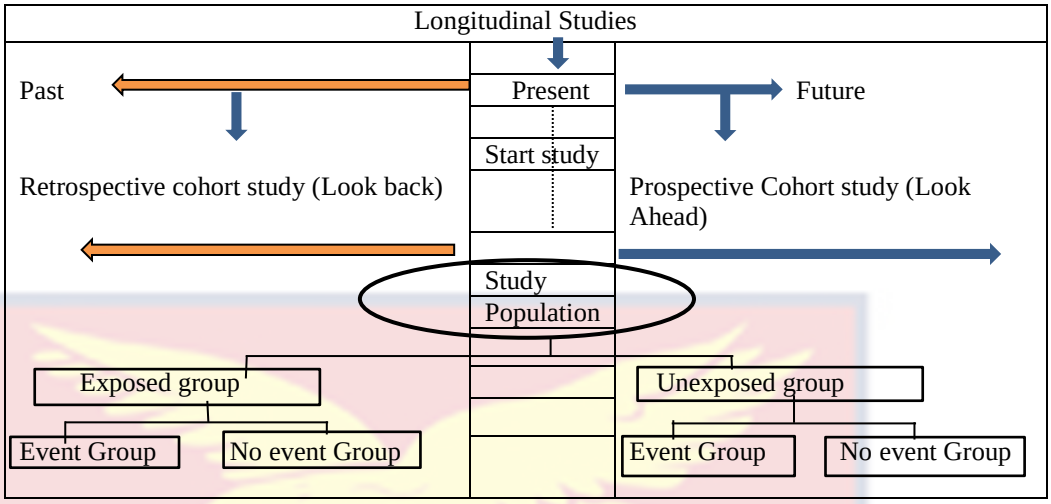

Figure 1: Conceptual Frame Work of Longitudinal Studies (Carter *et al*.,2012)

Benefits of Longitudinal Studies

1. There is a record of incident events: A prospective longitudinal study counts new cases of illness. It is possible to link the time of disease onset to recent changes in patient exposure as well as to long-term exposure.
2. Potential exposure determination: Participants in prospective studies can have many follow-up visits when their exposure status is recorded. This can reduce recall bias, which occurs when patients who later get an illness are more likely to remember their exposure (a form of measurement error). The time order of exposures and results is also noted.
3. Measuring how each person's results have changed. The ability to track changes in exposure and/or results at the individual level is one of a longitudinal study's primary advantages. The ability to spot unique patterns of change is made possible by longitudinal investigations.
4. Separation of cohort, period, and age effects throughout time. There are many different time scales to consider when examining changes over time. The age is equal to (period - cohort), for example, 58 = 2003-1945 and 40

= 2003-1963. The cohort scale is the time of birth, such as 1945 or 1963, the period is the current time, such as 2003. A longitudinal study with measurements at times $t_1, t_2, t_3, .. t_n$ can simultaneously characterize multiple time scales such as age and cohort effects using covariates derived from the calendar time of visit and the participant's birth year: the age of subject i at time t_j is $age_{ij} = (t_i -$ birth); and their cohort is simply $cohort_{ij} - birth_i$.

5. Take into account cohort effects. The comparison of subgroups of various ages in a cross-sectional study includes the impacts of aging with the effects of various cohorts. In other words, a comparison of 2003 results measured among 58-year-old subjects and 40-year-old subjects takes into account both the fact that the groups are 18 years older or younger (due to aging) and the fact that the subjects were born in various historical periods.

Challenges of Longitudinal Studies

1. Follow-up with participants: Due to inadequate follow-up or participant drop-out, there is a chance of bias. A naive analysis may produce summaries that are not representative of the original target population if individuals that are followed through to the scheduled end of the study differ from those who quit follow-up.
2. Analysis of correlated data: Statistical analysis of longitudinal data requires methods that can properly account for the intra-subject correlation of response measurements. If the such correlation is ignored then inferences such as statistical tests or confidence intervals can be grossly invalid.

3. Time-varying covariates: The direction of causality can be complicated by feedback between the outcome and the exposure, even if longitudinal designs give the chance to link changes in exposure with changes in the desired outcome. For instance, a patient's current health status may have an impact on the drug exposure or dosage received in the future in an observational research looking at how a medicine affects certain health markers. Notwithstanding the fact that the impact of medicine on health is of interest to scientists.

Characteristics of Longitudinal Studies

1. No interference: In longitudinal studies, the researcher makes no attempt to impede the participants' regular activities. A survey comprising both qualitative and quantitative questions is then administered by the researcher to gather their responses.
2. Observational: Observational studies entail keeping an eye on the research subjects over the course of the study and noting any changes in their characteristics that you see.
3. Timeline: A longitudinal study can be conducted over a period of weeks, months, years, or even decades. This stands in stark contrast to the results obtained from cross-sectional studies that are completed quickly.

Properties of Longitudinal Studies

1. Having repeated observations on individuals allows direct study of change (normal growth and aging).
2. Can separate aging effects (changes over time within individuals) from cohort effects (differences between subjects at baseline).

3. Require sophisticated statistical techniques since the repeated observations are usually correlated.
4. Certain types of correlation structures are likely to arise from this kind of data.
5. Correlation must be accounted for to obtain valid inference. Subjects serve as their own control which economizes on subjects and reduces unexplained variability in the response.
6. Robust to missing data and irregularly spaced measurement occasions (only if Mixed effect modeling was used).

Studies Using Multi-Stage Modeling

Multi-state models are a flexible tool for analyzing complex time-to-event problems with multiple endpoints, especially in chronic diseases where the patients move through different states. It provides a more detailed insight into the disease process as compared to other statistical models.

Multi-state models are particularly used in biomedical applications in which stages or levels of a disease are represented by the states in the model. A wide range of situations viz, in HIV/AIDS (Aalen *et al*., 1997, Grover *et al*., 2018, , Hendriks *et al*., 1998, Longini *et al*., 1989), breast cancer (Duffy *et al*., 1997, Putter *et al*., 2006), psoriatic arthritis (Cook *et al*., 2004, Keeffe *et al*., 2011), dementia (Joly *et al.*, 2002), diabetic retinopathy (Marshall and Jones 1995), and liver cirrhosis (Grover *et al*., 2018).

Putter *et al*. (2006) developed a multistate model for breast cancer patients to estimate transition rates between the states in the model and later used these estimates to predict the future progression of disease for patients with a given history. Taghipour *et al*. (2013) used a multistate model to

describe invasive breast cancer progression in the Canadian National Breast Screening Study and constructed progression models with and without covariates. They suggested that the modeling and estimating the parameters of cancer progression are essential steps towards evaluating the effectiveness of screening policies. Bro *et al*. (1999) used a multistate model to study prognostic factors associated with each transitions in breast cancer disease. Grover *et al*. (2018) used 131 application of multi-state Markov models for breast cancer progression to data from the first two rounds of the Florentine screening programme (1991-1993). Authors extensively discussed the pros and cons of three different estimation procedures (non-linear least squares, maximum likelihood, Bayesian approach) widely used in multistate model.

Chapter Summary

In Chapter Two, the review covers basic definitions and concepts of stroke, symptoms of stroke in both males and females, types of stroke and risk factors of stroke, treatment of stroke and medication. The literature reviw also covered stroke measurement scales such as, the Barthel index and National Institute of Health Stroke Scale. Some other issues covered incude the global prevelance of stroke and global burdern of stroke risks factors. We also compared the dynamics of stroke in Ghana to other countries in Sub-Sahara African and the world. Results from similar studies (risk factors of stroke) in stroke indicated that male to female ratio of incidence are similar, with female being slightly higher in isolated cases. The study adopted longitudinal design, as such literature was reiewed on benefits, challenges, characteristics, properties and studies using multi-state models.

Three main high risk factors of stroke were identified (increasing age, comorbidity and alcohol intake) during the review. Gaps that were identify during the review indicates that the focus so far has not been the estimation transition rate over diseases states.

CHAPTER THREE

METHODOLOGY

Introduction

In this study, Continuous Time Markov Chain (CTMC) models have been employed to observe the transition rates of stroke patients who were on rehabilitation at the Tamale Teaching Hospital (TTH) and monitored by the medical unit. Multi-stage CTMC was used to model the hazard rate of transitions among the states; *no stroke*, *mild*, *moderate*, *severe*, and *death*. We explored retrospective longitudinal studies to understand the relationship between the hazard rates and cdovariates over time (Mhoon *et al*., 2013). This study is necessitated because many researchers studied other cardiovascular accidents (CVA) ignoring stroke. There are few studies on the effect of some risk factors as in Baatiema *et al*. (2017), who indicated that income determines functional outcomes among stroke patients. Jones *et al*. (2000), Rost *et al*. (2016), and Lemmens (2018) predicted risk factors of stroke (age, gender, comorbidity factors, stroke type) using only initial counts on stroke severity. These predictable factors have not yet been studied over time. This research seeks to predict the transition rates of stroke patients over two monthly intervals of time for two years. The study also estimated the effect of some risk factors over time including the comorbidity factor. The model, CTMC in Multi-State Models (MSM) was used to estimate the average length of stay (mean sojourn time) of the various transient states.

In this chapter, the study provided a detailed methodology of the research by presenting it in systematic and logical procedures or techniques that would be used to select, process, and analyze information about the topic.

We have described the core points: design of this research, study area, data process, data set, model description, model formation, model assessment, data process and analysis, and then provide a summary to the chapter.

Study Design

In longitudinal studies of disease, CTMC models are generated to fit the progression of individuals through various illness states or stages. Subjects are monitored infrequently; typically, information is in the form of a health indicator or disease status at several distinct times in time (Mhoon *et al.*, 2013). For many subjects, it is typically difficult to determine the precise times when one illness state changes to another. Individual disease histories are often observed for a relatively small fraction (Combescure & Daur, 2002). Due to the difficulty in handling many intricate models, such as non-homogeneous Markov or semi-Markov models, one typically turns to time-homogeneous Markov models with straightforward transition topologies (Shoko & Chikobvu, 2018). Multi-state models are built in order to give a comprehensive perspective of the disease process and to enable estimation of the proportions of people who will be in each stage in the future. Furthermore, a continuous-time Markov model has been successfully applied to the stages of HIV infection and cancer (Grover, 2018) and does not necessitate making firm assumptions about the timing of illness development (Gentleman *et al.*, 1994, Mhoon *et al.*, 2013). Continuous-time Markov models have been used to simulate the occurrence of natural diseases for a very long period (Kalbfleisch & Lawless, 1985).

The need to address the challenges associated with stroke severity in the presence of comorbidity, other risk factors, and the state of a patient at a

particular time has prompted this study. The study also analyzed patients' history of stroke based on multi-state and death in a single model. However, survival models are not appropriate for all studies, particularly in the presence of competing risks and when multiple or recurrent outcomes are of interest (Shoko & Chikobvu, 2018). Markov models are relatively straightforward to analyze diseases state and death or loss of follow-up within a single model which survival models fail to do (Shoko & Chikobvu, 2018). Markov models can accommodate censored data, competing risks (informative censoring), multiple outcomes, recurrent outcomes, frailty, and constant survival probability. Examination of the conditions of the stochastic processes at various points in time, categorization of the conditions, and examination of the external influences on the stochastic processes can be done using Markov models (Bartolomeo, Trerotoli, & Serio, 2011). Markov models are favorable to the modeling of diseases in particular cases where the disease is grouped into a set of exhaustive and mutually exclusive health states, thereby forming a multi-state model (Shoko & Chikobvu, 2018). History is naturally generated as the multi-states evolve. It contains information on previous visits, time of entry into various states, and the length of stay in a state. Continuous-time homogeneous Markov models have been used since early in the epidemic to model disease progression of HIV/AIDS patients, and there has been some recent renewed interest in the use of these models.

Study Population

The study population includes stroke patients in the Northern, North East, Upper East, Upper West, and Savanna regions. According to the 2021 Population and Housing Census (PHC), the population of the five regions of

the study area is 5,825,290 (Savanna is 649,627, North East is 658,903, Upper West is 904,697, Upper East is 1,301,122 and Northern region is 2,310,943).

Data Set

A longitudinal study was adopted retrospectively for a cohort from January 2014 to December 2019. The study participants comprised of stroke patients (patients who had recovered from a past cerebrovascular accident and are receiving treatment) from the Medical Unit of the Tamale Teaching Hospital.

The Hospital serves all the five Northern regions in Ghana. Selection criteria included those individuals who had an initial or were referred for hospitalization for stroke from January 2014 to December 2019. Patients who died within 40 days of admission were excluded from the selection criterion. The main outcome measures were survival and discharge at home. Patients who survived the stroke were given rehabilitation therapy under the Medical Unit in the hospital. Monitoring of patients was done by the stroke unit. Disease progression was recorded at different two months-time intervals using the Modified Barthel Index (MBI). Patients who were lost to follow-up were also excluded from the data. The MBI is an outcome measure used to assess the progression of stroke. It measures the Functional Independence (FI) of the patients. MBI has 10 items on Activity of Daily living (ADL). The total score of 20 indicates full independence in the ADL; a higher score represents a higher level of independence (mild stroke). An $10 \leq MBI < 15$ usually represent moderate disability and MBI<10 indicates severe disability (Quinn *et al*., 2011). Monitoring the state of the disease was done at two monthly

equal intervals over a two year period. Some patients were lost to follow-up, some withdrew and some died.

We also used statistical modeling to approximate the impact of some risks factors on successive vascular events or death, taking into consideration prospective biases together with stroke severity, discharge destination, comorbidities, and time to initial treatment or cessation of treatment. The dataset also included information on the stroke event, treatment started or recommended at discharge, all dispensed medication at 2 monthly or less time points.

Model Description

If M individuals are involved in a longitudinal study and each subject is free to move between S different states in the study's state space of $1,2,3,\ldots,S$.

Let $y(t_m,k)$ be a representation of the stage's outcome at time point $T=(t_0,t_1,t_2,\ldots,t_m : t_0 = initialvisit, t_1 = 2\,months,\ldots,t_{12} = 24\,months)$, k for $m=1,2,\ldots,M$ and $k=1,2,\ldots K_m$, where K_m represents number of times observations have been made on the subject. Suppose the underlying process for each subject is a first-order homogeneous continuous-time Markov chain that is completely represented by the infinitesimal rate matrix.

$Q=\{q_{ij}\}$ where $q_{ij} \geq 0$ for $j \neq i$ and

$-q_{ii} = \sum_{i \neq j} q_{ij}$ for $i, j = 1,2,3,\ldots,S$.

We assume that the transition rate q_{ij} is constant across time and that the past and future states are independent of the present state. In this model, the amount of time a subject spends in a state i has an exponential distribution

with a mean of $1/q_{ii}$. Moreover, the transition rate q_{ij} can be understood as the hazard rate of i change from state i to state j, which can be computed as in competing risk models (Uebelacker, 2017). The transition probability for subject m moving from state i at time $t_m, k-1$ to state j at time t_m, k is defined as

$$p_{ij}(t) = \Pr\left[y(t_m, k) = j \,|\, y(t_m, k-1) = i \right]$$

Where

$$t = \left[(t_m, k) - (t_m, k-1) \right] \geq 0$$

For $i, j = 1,2,3,\ldots,S$ and $k = 1,2,3,\ldots K_m$.

$$P(0) = I$$

The $S \times S$ transition probability matrix

$$P(t) = \left\{ p_{ij}(t) \right\}$$

is determined by the infinitesimal rate matrix Q and can be expressed as

$$\boldsymbol{p}(\boldsymbol{t}) = \boldsymbol{e}^{\boldsymbol{Qt}} = \boldsymbol{I} + \sum_{\boldsymbol{k}=1}^{\infty} \frac{\boldsymbol{Q}^{\boldsymbol{k}} \boldsymbol{t}^{\boldsymbol{k}}}{\boldsymbol{k}!}$$

where I is the identity matrix.

A continuous time Markov model is fully defined by the computed matrix of probabilities for each state to be the next (sometimes referred to as the jump chain) and the mean sojourn periods in each state. Comparing this to a transition intensity matrix, it is a more meaningful and intuitive way to describe a model. According to an approximation, the matrix for the likelihoods that state j will be the subsequent state following state i is

$$p_{ij} = \frac{1}{4} \alpha_{ij} \lambda_{ij}$$

for each i and j such that $i \neq j$ and α_{ij}

is the force of transition from state i to state j and λ_{ij} is the total force of transition out of state i.

Informative sampling times

We must consider the reasons why observations were made at the specified dates to fit a model to longitudinal data with arbitrary sampling times. This is comparable to the issue of missing data, where the absence of a certain observation may imply information about the importance of that observation. Potential observational plans include:

Fixed: Each patient is monitored in this setting at predetermined fixed intervals.

Random: Regardless of the disease's current state, the sampling intervals change at random..

Doctor's Care: Patients with more serious illnesses receive closer monitoring. Based on the current disease state, the following sampling time is selected.

Patient Self-Selection: On occasion, a patient may prefer to go to the doctor even when they are not doing well (Jackson, 2019).

Continuous Time Markov Chain (CTMC)

A stochastic process $\{ X(t), t \geq 0 \}$ is a Continuous Time Markov Chain (CTMC) if, for all $s, t \geq 0$ and $X(t), t \geq 0$ nonnegative integers i, j, k

$$P\left[X(t+s) = j | X(s) = i, X(u) = k, 0 \leq u \leq s \right]$$

$$= P\left[X(t+s) = j | X(s) = i \right] \quad (1)$$

This means that in CTMC, the conditional probability of the future state at time $t+s$ given the present state at s and all past states depends only on the

present state and is independent of the past.

Time Homogeneous Markov Chain

If the

$$P\left[X\left(t+s\right)=j|X\left(s\right)=i\right]$$

is independent of s, then the process

$$X\left(t\right),t\geq 0$$

is said to be time homogeneous Markov Chain and have stationary (or homogeneous) transition probabilities.

If we let

$$p_{ij}\left(t\right)=P\left[X\left(t+s\right)=j|X\left(s\right)=i\right]$$

then,

$$p_{ij}\left(t\right)=P\left[X\left(t\right)=j\right] \tag{2}$$

That is $p_{ij}\left(t\right)$ is the probability that a Markov chain that is presently in state i will be state j after an additional time t, and $p_{ij}\left(t\right)$ are the transitional probability functions that satisfy the condition

$$0\leq p_{ij}\left(t\right)\leq 1.$$

Also,

$$\sum_{j}p_{ij}\left(t\right)=1 \tag{3}$$

$$\sum_{j}p_{j}\left(t\right)=1 \tag{4}$$

Equation (4) follows from the fact that at any time the process must be in some state.

Furthermore,

$$p_{ij}(t+s)=\sum_k P\left[X(t+s)=j, X(t)=k|X(0)=i\right]$$

$$=\sum_k\left\{\frac{P\left[X(0)=i, X(t)=k, X(t+s)=j\right]}{P\left[X(0)=i\right]}\right\}$$

$$=\sum_k\left\{\frac{P\left[X(0)=i, X(t)=k\right]}{P\left[X(0)=i\right]}\right\}\left\{\frac{P\left[X(0)=i, X(t)=k,\ X(t+s)=j\right]}{P\left[X(0)=i,\ X(t)=k\right]}\right\}$$

$$=\sum_k P\left[X(t)=k\middle|, X(0)=i\right]P\left[X(t+s)=j\middle|, X(0)=i, X(t)=k\right]$$

$$=\sum_k P\left[X(t)=k\middle|, X(0)=i\right]P\left[X(t+s)=j\middle|X(t)=k\right] \quad (5)$$

This equation is refer to as the Markov proper

$$=\sum_k p_{ik}(t)\,p_{kj}(s) \quad (6)$$

And Equation (6) is called the Chapman-Kolmogorov for CTMC. Suppose that we define the matrix of $p_{ij}(t)$ as

$$P_{ij}(t)=\begin{bmatrix} q_{11}(t) & q_{12}(t) & q_{13}(t) & q_{14}(t) & q_{15}(t) \\ q_{21}(t) & q_{22}(t) & q_{23}(t) & q_{24}(t) & q_{25}(t) \\ q_{31}(t) & q_{32}(t) & q_{33}(t) & q_{34}(t) & q_{35}(t) \\ q_{41}(t) & q_{42}(t) & q_{43}(t) & q_{44}(t) & q_{45}(t) \end{bmatrix}$$

Then the Chapman-Kolmogorov equation becomes

$$P(t+s)=P(t)P(s) \quad (7)$$

Whenever a CTMC enters a state i, it spends an amount of time $\frac{1}{vi}$ called the dwell time (or holding time) in that state. The holding time in state is exponentially distributed with mean $(\frac{1}{-q})$. At the expiration of the holding time, the process makes a transition to another state j with probability p_{ij}, where

$$\sum_k p_{ij} = 1 \tag{8}$$

Because the mean holding time in state i is $\frac{1}{v_i}$, v_i represent the rate at which the process leaves state i and $v_i p_{ij}$ represents the rate when in state i that the process makes a transition to state j. Also, because the holding times are exponentially distributed, the probability that when the process is in state i a transition to state $j \neq i$ will take place in the next small time Δt is $v_i p_{ij} \Delta t$. The probability that no transition out of state i will take place in Δt given that the process is presently in state i is

$$1 - \sum_{j \neq i} p_{ij} v_i \Delta t \, i$$

and

$\sum_{j \neq i} p_{ij} v_i \Delta t$ is the probability that it leaves state i in Δt.

State Transition for Markov Chain Process

Considering the transition equations for state i for small time interval Δt, we obtain the following equations:

$$p_i(t + \Delta t) = p_i(t)\left\{1 - \sum_{j \neq i} p_{ij} v_i \Delta t\right\} + \sum_{j \neq i} p_j(t)\, p_{ji} v_j \Delta t$$

Thus

$$p_i(t + \Delta t) - p_i(t) = -p_i(t) \sum_{j \neq i} p_{ij} v_i \Delta t + \sum_{j \neq i} p_j(t)\, p_{ji} v_j \Delta t$$

$$\frac{p_i(t + \Delta t) - p_i(t)}{\Delta t} = -v_i p_i(t) \sum_{j \neq i} p_{ij} v_i + \sum_{j \neq i} p_j(t)\, p_{ji} v_j \tag{9}$$

$$\lim_{\Delta t \to 0}\left\{\frac{p_i(t + \Delta t) - p_i(t)}{\Delta t}\right\} = \frac{dp_i(t)}{dt} = -v_i p_i(t) \sum_{j \neq i} p_{ij} v_i + \sum_{j \neq i} p_j(t)\, p_{ji} v_j$$

In the steady state,

$$p_i(t)\Delta t p_j \text{ and}$$

$$\lim_{\Delta t \to 0}\left\{\frac{dp_i(t)}{dt}\right\} = 0 \tag{10}$$

Thus, we obtain

$$-v_i p_i(t)\sum_{j\neq i} p_{ij} + \sum_{j\neq i} p_j(t)\, p_{ji} v_j = 0$$

$$\sum_i p_i = 1$$

$$v_i p_i(t)\sum_{j\neq i} p_{ij} = \sum_{j\neq i} p_j(t)\, p_{ji} v_j \tag{11}$$

Alternatively, we can write

$$\sum_i p_i = 1 \tag{12}$$

The right-side line of Equation (12) is the rate of transition out of i, while the left side is the rate of transition into i. Equation (12) states that in a steady state, the two rates are equal for any state in the Markov chain.

Transient Analysis

We note from Equation (9) that

$$\frac{dp_i(t)}{dt} = -v_i p_i(t)\sum_{j\neq i} p_{ij} v_i + \sum_{j\neq i} p_j(t)\, p_{ji} v_j$$

We define the following parameters

$$q_{ji} = p_{ji} v_j$$

$$q_i = v_i \sum_{j\neq i} p_{ij} = \sum_{j\neq i} q_{ij}$$

Then Equation (4) becomes

$$\frac{dp_i(t)}{dt} = -q_i p_i(t) + \sum_{j \neq i} p_j(t) q_{ji} \tag{13}$$

$$p(t) = \left[p_1(t), p_2(t), p_3(t), \ldots \right]$$

We further define the following vectors and matrix:

$$\frac{dp(t)}{dt} = \left[\frac{dp_1(t)}{dt}, \frac{dp_2(t)}{dt}, \frac{dp_3(t)}{dt}, \ldots \right]$$

$$Q = \begin{bmatrix} q_{11}(t) & q_{12}(t) & q_{13}(t) & q_{14}(t) & q_{15}(t) \\ q_{21}(t) & q_{22}(t) & q_{23}(t) & q_{24}(t) & q_{25}(t) \\ q_{31}(t) & q_{32}(t) & q_{33}(t) & q_{34}(t) & q_{35}(t) \\ q_{41}(t) & q_{42}(t) & q_{43}(t) & q_{44}(t) & q_{45}(t) \end{bmatrix}$$

Then Equation (5) becomes

$$\frac{dp(t)}{dt} = p(t)Q \tag{14}$$

Q is usually called infinitesimal generator matrix or (intensity matrix). Under the initial condition that $p(0) = I$, where I is the identity matrix, the solution to this matrix equation is

$$p(t) = e^{Qt} = I + \sum_{k=1}^{\infty} \frac{Q^k t^k}{k!} \tag{15}$$

(Ibe, 2013)

Model Formation

At any time (Δt), the state of the individual patient is defined base on no stroke, mild stroke, moderate stroke, severe stroke or whether the individual is dead as follows; Basing on these five states, progression of stroke among patients on treatment could be defined by the state diagram below. The arrows in the diagram show possible transition between the five states.

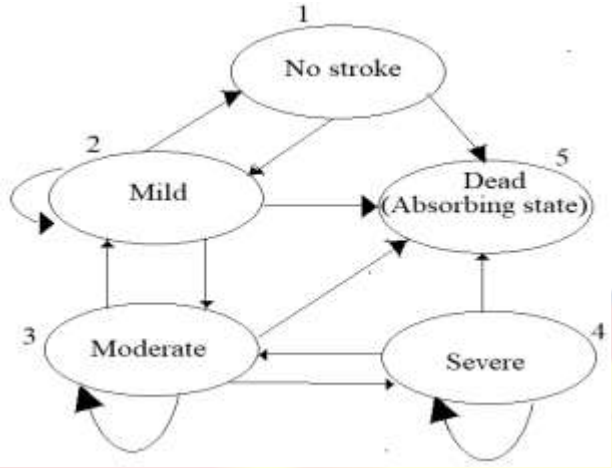

Figure 2: General Transition Diagram
Author's Construct (2023)

The transition states in the figure 2 shows the various diseases state of stroke patients on rehabilitation. State 1 (no stroke), state 2 (mild stroke), state 3 (moderate stroke) and state 5 is an absorbing state (death) hence there are no transitions from this state to any other state.

As stroke progresses in an individual, there is a possibility of an individual being in the same state in consecutive visit. The possible transition counts that took place for the whole period of study 2014 to 2019 can be explained as; the transition count from state i to $i \pm j$ are higher for all the values in which $j = i + 1$ than for $j = i - 1$ where $i, j \grave{o} i \left(2,3,4\right)$ are transient states. A model would be formulated based on the assumption that between times $(t, t + \Delta t)$, where t is a very small value, there is a transition from anyone of the states $i = 2, 3, 4$ (transient states) to state $j = 1, 2, 3, 4, 5$ defined as follows:

1. An individual can remain in the same state at a rate of

   $a_{ij} = -\lambda_i = -(a_{i,i-1} + a_{i,i+1} + a_{i5})$, α_{ij} is the force of transition from state i to state .

2. Some individuals fail to adhere to treatment therapy. These individuals can transit to a state of higher severity at a rate of q_{ij} where $j = i+1$
3. Some individuals may adhere to treatment therapy. These individuals can transit to a state of low severity at a rate of q_{ij} where $j = i-1$
4. An individual in state $i = 1,2,3,4$ can die (state 5, absorbent state) at a rate of q_{i5}.

This is based on the fact that the sum of transition rates from any state is equal to zero. These assumptions can be characterized by the following transition rate matrix $Q(t)$.

$$Q = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ q_{21} & -(q_{21}+q_{25}) & 0 & 0 & q_{25} \\ q_{31} & q_{32} & -(q_{31}+q_{32}+q_{35}) & 0 & q_{35} \\ 0 & 0 & q_{43} & -(q_{43}+q_{45}) & q_{45} \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

Properties of Infinitesimal Transition Matrix

The basic data specifying a continuous-time Markov chain is contained in a matrix $Q = (q_{ij}), i, j \grave{o} S$, which we will sometimes refer to as the infinitesimal generator, or the $Q-matrix$ of the process, where S is the state set. This is defined by the following properties:

1. $q_{ii} \leq 0$ for all $i \grave{o} S$;
2. $q_{ij} \geq 0$ for all $i, j \grave{o} S$ such that $i \neq j$;
3. $\sum_{j \in S} q_{ij} = 0$ for all $i \grave{o} S$.

The Expected Holding Time

The expected holding time in each state, also known as the mean sojourn time a patient spent in each state, is a single stay before he or she makes a transition to another state. The mean sojourn time in each state i for $i = 1, 2, 3, 4$ is estimated as

$$\frac{1}{\lambda},$$

where $\lambda_i = \sum_{i \neq j} a_{ij}$ is the total force of transition out of state i.

The Jump Chain

The jump chain is when a Markov process is observed at the times it makes transition to a new state. In other words, a jump chain is a stochastic matrix Q of probabilities where each row sum up to one, on the state space X_t, which gives the conditional probability of the next stage an individual goes to after leaving state i. If $a_{ii} > 0$ then given that there is a jump to a different state, it means we never stay in state i, we make a jump out resulting in having $Q_{ii} = 0$ and if $a_{ii} = 0$, then we never leave state i meaning that $a_{ii} = 1$ (state 5). The matrix for the probabilities that the next state after state i is approximated as,

$$p_{ij} = \frac{a_{ij}}{\lambda_i}$$

for each i and j such that $i \neq j$, a_{ij} is the force of transition out of state.

Total Length of Stay

The total length of stay, often known as mean sojourn times, refers to the typical amount of time spent in a state. We may want to predict the overall

amount of time spent healthy or ill, before death, for processes with repeating periods of recovery and relapse. We estimate the forecasted total length of time spent in each transient state between two future time points t_1, for a given set of covariate values. This defaults to the expected amount of time spent in each state between the start of the process (time 0, the present time) and death or a specified future time.

The Incorporation of Covariates

In practice, there are measured covariates on each individual under study, and more attention is on the relationship between these covariates and the intensities q_{ij} in the Markov model. The Markov model can be extended in a straight forward way to allow for regression modeling of Q. If we assume that the proportional intensities can be expressed as

$$q_{ij}(z) = q_{ij}\exp\left\{\mathrm{B}_{ij}^{1} z(t)\right\} \qquad i \neq j \tag{16}$$

where $\boldsymbol{Z}$ is the s dimensional vector of covariate;

$\boldsymbol{B_{ij}}$ is a vector of s regression parameters relating the instantaneous rate of transitions from state i to state j to the $\boldsymbol{B_{ij}'s}$ covariate and $q_{ij0}(z)$ represents the baseline intensity relating to the transition from state i to state j. The resulting transition $q_{ij}(\boldsymbol{z})$ intensity matrix $Q(\boldsymbol{z})$ for a subject with vector of covariates $\boldsymbol{Z}$ with elements can be used in Equations (1) and (2) to compute the transition probability matrix $P(t\,|\boldsymbol{z})$: The elements $p_{ij}(t\,|\boldsymbol{z})$ of this transition probability matrix constitute the contribution of each observation to the likelihood function

$$q_{ij}(z) = q_{ij0}\exp\left\{\mathrm{B}_{ij}^{1} z(t)\right\} \qquad i \neq j \tag{17}$$

A log-linear model for the Markov rates $\boldsymbol{q_{ij}(z)}$ is chosen primarily for analytical convenience and because this model has the attractive feature of yielding nonnegative transition intensities for any $\boldsymbol{Z}$ and other parameterizations may be more appropriate in particular applications. Moreover, modeling on related scales such as log-hazard makes it possible to study the way that the baseline probabilities are modified by covariates. The log-linear model which nearly makes it possible to interpret in a convenient way the value of the coefficient $\boldsymbol{B_{ijk}}$ which is not always the case with other models. Note that an increasing number of covariates can make computation too extensive to be easily implemented. Indeed $i \to j$, an increase in the number of covariates (or regression coefficients) requires more information in the data and more computational resources because the likelihood becomes very difficult to compute.

The effect of covariate vector $\boldsymbol{Z}$ on transition for a stroke patient is modeled by $q_{ij}(t)$ using Cox proportional regression model the transition hazard is given by

$$q_{ij}(t \mid z) = q_{ij0}(\mathrm{t}) \exp\left\{\mathrm{B}_{\mathrm{ij}}^{T} z\right\} \qquad i \neq j$$

where $q_{ij0}(\mathrm{t})$ is the baseline hazard of transition i and j and B_{ij} is the vector of the regression coefficients that describe $\boldsymbol{Z}$ the effect on transition i and j.

An alternative way of writing this model is

$$q_{ij}(t \mid z) = q_{ij0}(\mathrm{t}) \exp\left\{\mathrm{B}_{\mathrm{ij}}^{T} z_{ij}\right\} \qquad i \neq j$$

where z_{ij} is a vector covariates specific to transition $i \to j$, defined for the patient based on his or her covariates $\boldsymbol{Z}$. The estimates $\hat{B}$ can be obtained by maximizing the partial likelihood function.

$$L(\beta) = \prod_{k=l}^{n} \frac{\exp\left\{B_{ij}^{T} z_{ij}\right\}}{\sum_{l \grave{o} R(t_{ij,k})} \exp\left\{B_{ij}^{T} z_{ij,l}\right\}} \tag{18}$$

where $z_{ij,k}$, the covariate vector is for patient *k* and $R(t_{ijk})$ is the risk set a time for making transition from $i \to j$ (Grover *et al*., 2018) and (John, Michael & Ackerman, 2008).

Likelihood Ratio and Wald Tests

Goodness-of-fit Tests

We use prevalence counts to perform a goodness-of-fit test for the suggested model in this study (Wan, 2016). The prevalence counts serve as an ad hoc empirical indicator of state population density. The expected state occupancy rates predicted by the fitted model should be close to the observed state occupancy rates if the model fits the data well. We may assess the fitted model's general goodness-of-fit by comparing observed and expected prevalence counts (Wan, 2016).

Data Visualization and Analysis

Patient variables included in the study data are: *patient number*, *age*, *sex*, *marital status*, *religion*, *educational status*, *occupation*, *location of patient*, *comorbidity type*, *local treatment*, *smoking*, *alcohol intake*, and *rehabilitation type* (on drugs, on exercise, or on both). Patients with less than three visits were excluded from the study. Each patient's number of visits to the facility was recorded. The medical officer indicated the condition of each

patient at a particular time. The multi-state model in the package was used to model the transition rates. We coded the data and imported it into the package. The ages of the patients were grouped as youth (15–45), old (46–60), and older (61 or more). Thus, age was coded as

$$\text{Age} = \begin{cases} youth\left(15-45 \text{ years}\right), & 0 \\ old\left(46-60 \text{ years}\right), & 1 \\ older\left(61 \text{ years and over}\right), & 2 \end{cases}$$

Coding for sex was as follows:

$$\text{Sex} = \begin{cases} male, & 0 \\ female, & 1 \end{cases}$$

Religion was coded as

$$\text{Religion} = \begin{cases} \text{islam}, & 0 \\ \text{christianity}, & 1 \end{cases}$$

Marital status was also one of the covariates we expressed an interest in and was coded as follows:

$$\text{Marital status} = \begin{cases} single, & 0 \\ widowed, & 1 \\ married, & 2 \end{cases}$$

Patients were engaged in different occupations before the onset of stroke. Thus, occupation was coded as follows:

$$\text{Occupation} = \begin{cases} civil\ Servant, & 0 \\ self\ employed, & 1 \\ houseWife, & 2 \\ others, & 3 \end{cases}$$

Some patients received local treatment prior to their first visit and during rehabilitation, whereas others only received hospital rehabilitation:

The teaching hospital is a referral unit in northern Ghana, and patients were referred to this facility from different locations in the north. On record, we have the following:

$$\text{Location} = \begin{cases} \text{Upper East}, & 0 \\ \text{Northern}, & 1 \\ \text{North East}, & 2 \\ \text{Savanna}, & 3 \\ \text{Upper West}, & 4 \end{cases}$$

We also assessed the effect of comorbidity on a patient's recovery rate. Stroke patients surviving with other diseases were noted. Patients with only hypertension, hypertension/diabetes, and no comorbidity were noted as.

$$\text{Comorbidity} = \begin{cases} hypertension, & 0 \\ hypertension\ and\ diabetes, & 1 \\ no\ comorbidity, & 2 \end{cases}$$

Patients were advised not to take alcohol during rehabilitation. Some got addicted to alcohol and were coded as

$$\text{Alcohol intake} = \begin{cases} no\ Alcohol, & 0 \\ addicted\ to\ Alcohol, & 1 \end{cases}$$

Patients who were onto smoking were advised to quit smoking in order to improve rehabilitation.

Patient's severity status was recorded on arrival. We considered coding diseases as free, mild, moderate, severe, and death.

$$\text{Disease state} = \begin{cases} disease\ free & 1 \\ mild\ state & 2 \\ moderate\ state & 3 \\ severe\ state & 4 \\ death\ state & 5 \end{cases}$$

In preparing the data for analysis, we installed the **msm** package from the CRAN archive in the console (version 4.1.0). Data in an Excel sheet was put in long format (data frame) to enable the package to run it. The time of observations and the observed states for the process were: state 1 (disease free), state 2 (patients with mild stroke), state 3 (patients with moderate stroke), state 4 (patients with severe stroke), and state 5 (patients who died during the study period or who withdrew from the study). The excel file was saved in **CSV** format to enable reading of the data by the console.

The first output was to display a sample of the data in long format. Our second result displayed the summaries of the multi-state, indicating the number of individuals in the various states. This output defines our matrix. (Q). To tell **MSM** what the allowed transitions of the model are, we define a matrix of the same size as containing zeros in the positions where the entries are zeros. All other positions contain an initial value for the corresponding transition intensity. The diagonal matrix would also be assigned zeros. In the model, this diagonal matrix entry is defined as the minus of the sum of all entries in the row (a unique property of the infinitesimal generator matrix).

Our next analysis was estimates for the main model (model 1 = illness-to-death). This result shows the baseline transition intensities among the various states. In order to determine the effect of the covariates on the transition rates, we ran the data for each covariate. We first compared the model 1 transition rate with the baseline rates for the covariate. If the covariate baseline rates indicate some effects (with transition rates less than 1), we go ahead and estimate the rates for each level of the factors. When the baseline rates of the covariates are greater than or equal to 1 (indicating no contribution

of the covariate), all the rates for the levels of that factor are estimated at rates greater than or equal to 1 (Jackson, 2019). We conclude that the covariate has no significant effect on the transition rates of the stroke patients. We also estimated the mean sojourn time of transient states. Our final analysis was a model assessment. We estimated the expected frequencies and percentages and compared these estimates with the observed frequencies and percentages. These expected and observed frequencies were used to fit the survival plots of all the states over time.

Chapter Summary

We explored retrospective longitudinal studies to study the relationship between the hazard rates and covariates over time (Mhoon *et al*., 2013). This study was necessitated because many researchers studied other cardiovascular accidents (CVA) while ignoring stroke. There are few studies on the effect of some risk factors, as in Baatiema *et al*. (2017), who indicated that income determines functional outcomes among stroke patients. Jones *et al*. (2000), Rost *et al*. (2016), and Lemmens (2018) used the initial counts on stroke severity in predicting risk factors for stroke (age, gender, comorbidity factors, stroke type). In this chapter, we have described the design we employed for the study, including the advantages and disadvantages. We also narrated how the data was sourced from the study area and described the data set in detail, and the concept of CTMC gave us a better understanding of how diseases progress. The modelling concept included how transitions took place among the stroke patients at the various states. We saw how the covariates are incorporated into the main model and the effect of the covariates on recovery.

A model diagnosis was done using the goodness-of-fit test to assess how well the observed data fit the expected prevalence count.

CHAPTER FOUR

RESULTS AND DISCUSSION

Introduction

The research seeks to address how stroke patients progress to death or recover from stroke under rehabilitation at the Tamale Teaching Hospital. We employed CTMC in MSM to observe the transition rates of the patients at two (2) monthly intervals for two years. The reason for using this model is to provide a detailed view of stroke recovery. We want to estimate the proportion of persons that will transit to different states at various points in time ($t_1 = 2 months, t_2 = 4 months, t_3 = 6 months, \ldots, t_{12} = 24 months$).The study aimed to address the challenges posed by comorbidities, stroke severity, smoking, and other specific risk factors that affect stroke patients at different stages of their illness. The model will also estimate the average length of time patients stay in the various transient states before transitioning to less severe states. This will help inform health personnel of the state of rehabilitation at TTH.

First of all, we displayed the output and interpretations of results using descriptive statistics. The transition rates in our model included the following covariates: sex (male, female), age groups (youth, older, and older), comorbidity effect local treatment, alcohol use, smoking, which would also be estimated. The minimum, average, and maximum lengths of stay in the transient states were estimated. Finally, we performed model diagnosis using the observed and expected frequencies. These frequencies are used to plot survival rates at the various states.

Descriptive Statistics

The study provide concise summary of our data. Table 3 displayed the frequencies and percentages of our covariates (age group, sex, religion, marital status, occupation, local treatment, and location of patient, alcohol intake, smoking, comorbidity type and stroke severity status on admission.

Table 3: Frequency Distribution of Patients on Rehabilitation

FACTOR	CODE	FFREQUENCY	PERCENTAGE
Age	Youth (≤ 45) = 0	9	21.6
	Old ($45<age\leq 60$) = 1	13	37.1
	Older (>60) = 2	15	41.3
Sex	Male (0)	14	37.8
	Female (1)	23	62.2
Religion	Islamic (0)	24	35.1
	Christianity (1)	13	64.9
Marital status	Single (0)	1	2.7
	Married (1)	33	89.2
	Widowed (2)	3	8.1
Occupation	Civil servant (0)	6	16.2
	Self Employed (1)	16	42.2
	House wife (2)	4	10.8
	AGRA Ghana (3)	1	2.7
	Other (4)	10	27
Local Treatment	Yes (1)	15	40.5
	No (0)	22	59.5
Location	Upper East (0)	5	13.5
	Northern Region (1)	22	59.5

Table 3:Cont.

	North East (2)	5	13.5
	Savanna Region (3)	4	10.8
	Upper West (4)	1	2.7
Comorbidity	Hypertension (0)	14	37.8
	Hypertension/diabetes(1)	8	18.9
	No comorbidity (2)	15	40.5
Alcohol	Yes (0)	2	5.4
	No (1)	35	94.6
Smoking	Yes (1)	3	8.1
	No (0)	34	91.9
Stroke status	Mild	4	10.8
	Moderate	14	37.8
	Severe	19	51.4

Author's Construct (2023)

Table 3 shows the frequency distribution of stroke patients who were in rehabilitation at TTH. Thirty-seven (37) were followed up during the study. Table 3 above indicated that, among the age groups, patients within the youth group (n = 9) were the least in the study. The majority of the patients belong to the older age group (15). Female patients (23) also outweigh male patients (14). A patient was either Christian (age 13) or of Islamic religion (age 24). Only one (1) patient was single; three (3) were widowed, and the majority (33) were married. Four (4) patients were housewives, and the rest had at least one type of job for survival: teacher (4), civil servant (1), trader (9), farmer (4), driver (2), nurse (1), plumber (1), ARIED Ghana (1), stroke keeper (1), and nine (9) had no history of occupation. Fifteen patients combine treatment with rehabilitation, while 22 patients stick to rehabilitation measures. Most of the patients were aware of some of the stroke risk factors, as only a few (three)

went on to smoke and the rest (34), were aware of smoking. Thirty-five (35) patients reported not taking alcohol, while two (2) patients could not fail to take it. All the patients report coming from one of the five regions: the Northern (22), Upper East (5), Upper West (1), North East (5), and Savannah region (4). While 14 patients were living with hypertension, eight (8) patients were living with diabetes and hypertension, and fifteen (15) were free from any other diseases. Patients on admission had different severity levels. Four (4) patients were diagnosed with a mild stroke; fourteen (14) patients had a moderate stroke, and the majority (19) were diagnosed with a severe stroke.

Transition Analysis

This illustrates the changes over the two-year time period that our CTMC described. The model contains both backwards and forwards transitions. This model is essential because it will help us understand how quickly participants transition into new states and how quickly they will transition into different states in the future based on how long they spend in their present states. Non-adherence to treatment may result in a transition to a more severe state, while patients who adhere to treatment may experience an early recovery. Table 4 presents transition distributions.

Table 4: Transition Distributions

State	No (1)	Mild (2)	Moderate (3)	Severe (4)	Death (5)
Mild (2)	13	128	9	1	4
Moderate (3)	0	35	54	12	4
Severe (4)	0	2	27	18	3
Death (5)	0	0	0	0	0

Author's Construct (2023)

Table 4 shows the transition distributions of the disease among the five states: no stroke, mild, moderate, severe, and death. The table revealed that 13 patients had transited from a mild to a disease-free state at the end of the two years. Nine (9) patients transitioned from mild to moderate stroke. 128 patients transited or were retained in the mild state, while one patient transited to a more severe state. Thirty-five (35) patients in a moderate state recovered to a mild state; twelve (12) patients had developed a severe stroke; and 54 patients maintained or transited to a moderate state. Of the 19 patients who had a severe stroke, two recovered to mild, and 18 probably had not adhered to treatment (severe). Thus, there were four (4) deaths from mild stroke, two (2) deaths from moderate stroke, and three (3) deaths from severe stroke. Patients who were admitted with more severe stroke never recovered during the two years of study.

Transition Intensity Matrix

An array of numbers indicating the instantaneous rate at which a CTMC transit between states is referred to as a transition rate matrix, also known as an intensity matrix or an infinitesimal generator matrix. In a infinitesimal generator matrix with element q_{ij} for $i \neq j$ represents the rate Q departing from i and entering in state j. The transverse elements q_{ij} can be well-defined as

$$q_{ii} = -\sum_{j \neq i} q_{ii}$$

and satisfied the following conditions:

$$0 \leq -q_{ii} \leq \infty$$

$$0 \leq q_{ij} : \text{for} \, i \neq j$$

$$\sum_{j \neq i} q_{ij} = 0 : \text{for} \, all \, i$$

The outcome of this rate matrix is shown in Table 5 below

Table 5: Model 1 Transition Intensity Matrix

	State 1	State 2	State 3	State 4	State 5
State 2	0.079 (0.05, 0.13)	-0.196(-0.29, - 0.13)	0.085 (0.05, 0.16)	0	0.031 (0.01, 0.08)
State 3	0.0004 (0.001,Inf)	0.435 (0.31, 0.62)	-0.716 (-0.98, -0.52)	0.28 (0.15, 0.52)	0.00004 (0.00, 1.72)
State 4	0	0.0001 (-0.01, Inf)	1.011 (0.65 1.56)	-1.11 (-1.7, -0.73)	0.094 (0.02, 0.35)
State 5	0	0	0	0	0

Author's Construct (2023)

Table 5 displays the estimated transition ratios (together with 95% confidence intervals, in parenthesis) for two-year periods. The result indicated that a patient with a mild stroke (state 2) has a 0.07965 rate of recovery from stroke, a 0.0855 rate of transiting to a moderate stroke (state 3), and about a 0.03108 rate of being dead. Similarly, a patient with a moderate stroke (state 3) has a lower risk (0.0000004) of total recovery from state 3. But a patient with a moderate stroke who adhered to treatment has a higher rate (0.4357) of transiting to a less severe state compared to a 0.2804 risk of developing a severe stroke after the 2 years of follow-up. Finally, a patient with a severe stroke (state 4) never transited to a disease-free state, has little or no risk (0.000001) of transiting to a mild state, has no indication of being moderate (state 3), and could die with a transition rate of 0.0822.

Transition Rates for Covariates

Using a proportional intensities model, the study attempt to predict how the independent factors will affect the pace of transition. If we have an intensity matrix $Q(z)$ which depend on the covariate vector $\boldsymbol{Z}$, the transition intensity for patient i at observation time j is $q_{rs}\left(z_{ij}\right)=q_{ij}^{(0)}\exp\left(\beta_{rs}^{T}z_{ij}\right)$. The size of some of the hazard ratios' confidence intervals indicates that there may be no information about the covariate effect in the data, which results in a probability that is a flat function of the characteristics. Table 6 below displays the covariate transition rate compared with the baseline rates.

Table 6: Hazard Rate for Sex

	Baseline	Sex
State 2- State 1	0.0799 (0.040289, 0.1252)	1.1042 (0.39118, 4.331)
State 2- State 2	-0.1916 (-2.859, -0.1496)	–
State 2- State 3	0.0823 (0.041619, 0.1560)	0.6794 (0.13419, 3.143)
State 2- State 5	0.0292 (0.032846, 0.1244)	2.536 (0.57790, 8.359)
State 3- State 1	0.0000001 (0.00, Inf)	0.8019 (0.00000, Inf)
State 3- State 2	0.4374 (0.312, 0.6165)	0.6917 (0.35267, 1.575)
State 3- State 3	-0.7217 (-0.3142, 0.6145)	–
State 3- State 4	0.2811 (0.1462, 0.5406)	0.7242 (0.20566, 3.147
State 3- State 5	0.003 (-0.000, Inf)	0.8519 (0.000, Inf)
State 4- State 2	0.00000002 (0.00, Inf)	0.9821 (0.00000, Inf)
State 4- State 3	1.035 (0.653360, 1.6954)	0.7616 (0.3028, 1.915)
State 4- State 4	-1.107 (-1.702, -0.7204)	–
State 4- State 5	0.0717 (0.0051, 0.998)	2.59(0.02026, 2037)

Author's Construct (2023)

Table 6 compares the transition rates (and 95% confidence intervals) between the baseline and the effect of the factor sex. The table shows that the sex effect on transiting from the mild state (2) to the absorbing state is about

2.29 times more likely (2.5366/1.1043) than transiting to stroke-free as compared to the baseline rate. A patient admitted with or transiting to a moderate stroke has a very low rate (0.0000001) of recovery, but the gender type could influence recovery by a 0.6917 rate to a mild state. Gender could further improve total recovery with a transition rate of 0.8019 and a better rate of transiting to a less severe state. The baseline data shows no indication of a patient in a severe state transiting to a less severe state, but a patient's sex type could predict a 0.7616 rate of changing to a less severe state (3). These results may suggest that one of the sex types could improve recovery more than the other.

Covariate Effect of Male Compared to Female

Results of the study indicated in Table 6 that, there is a covariate differences between the various states. The study proceeded to check out which of the covariates actually increased or decrease the rate of recovery over the 2-year period. This result is shown in Table 7 below.

Table 7: Covariates Effect for Male and Female

	State 1	State 2	State 3	State 4	State 5
			Male		
State 2	0.077 (0.04, 0.15)	-0.197 (-0.31, 0.12)	0.098 (0.05, 0.18)	0	0.021 (0.02, 0.12)
State 3	0.0000001	0.494 (0.13, 0.62)	-0.81 (-1.2, -0.54)	0.313 (0.15, 0.69)	0.0034 (0.00, inf)
State 4	0.000001	0.00002	1.133 (0.64, 2.01)	-1.186 (-2.03, 0.68)	0.052 (0.002, 0.68)
State 5	0	0	0	0	0
			Female		
	State 1	State 2	State 3	State 4	State 5
State 1	0	0	0	0	0
State 2	0.085 (0.03, 0.13)	-0.198 (-0.4, -0.09)	0.057 (0.01, 0.23)	0	0.054 (0.03, 0.30)
State 3	0.0009	0.341 (0.18, 0.68)	-0.571 (-0.99,-0.32)	0.22 (0.07, 0.69)	0.003 (0.00, inf)
State 4	0.0000023	0.0000021	0.863 (0.42, 1.75)	-0.99 (-1.8, -0.5)	0.13 (0.01, 4.71)
State 5	0	0	0	0	0

Author's Construct (2023)

Table 7 compares the transition rates between male and female patients. The results revealed that female patients in a mild state have a higher rate (0.08538) of total recovery than their male counterparts (0.07732). They also indicate a lower rate of change of transiting to a more severe (moderate) state (0.05783) as compared to the rate of 0.09802 for males. While male patients in a severe state could transition to a moderate state 1.3 times

(1.133/0.863 = 1.312) faster than their female counterparts, Also, female patients stay longer in a severe state (1/0.985) than males (1/0.186). Thus, female patients indicated a higher rate of dying at states 2 and 4 (state 2 = 0.05483, state 3 = 0.0029, and state 4 = 0.1355) compared to males (state 2 = 0.02161, state 3 = 0.0034, and state 4 = 0.0523), but very similar rates at state three (3).

Transition Intensities for Age

This refer to the rate at which individuals in a particular age group move from one state or condition to another. These can include transitions such as entering or changes in health status. Age is an important factor in determining transition intensities, as the likelihood of experiencing certain events or transitions may vary significantly across different age groups.

Understanding transition intensities for different age groups can be important for a variety of purposes, including predicting future demographic trends, developing social policies and programs, and planning for retirement or other life transitions. Additionally, as the population ages and life expectancies increase, accurate modeling of age-related transitions becomes even more critical for ensuring the financial sustainability of insurance and pension plans. However, Table 8 displays the transition intensities between two or more states.

Table 8: Transition Intensities for Age (Youth Compared with Old)

	State 1	State 2	State 3	State 4	State 5
			YOUTH		
State 2	0.052 (0.02, 0.2)	-0.295 (-0.5, -0.2)	0.0978 (0.01, 0.3)	0	0.1448 (0.06, 0.3)
State 3	0.00012 (0.0, inf)	0.643 (0.3, 1.1)	-0.655 (-1.1, -0.4)	0.01 (0.001, 0.2)	0.00042 (0.0, inf)
State 4	0	0	0.83 (0.08, 0.2)	-0.83 (-1.6,-0.4)	0.00000002 (0.0, inf)
State 5	0	0	0	0	0
			OLD		
	State 1	State 2	State 3	State 4	State 5
State 2	0.067 (0.03, 0.1)	-0.21 (-0.3,-0.1)	0.085 (0.03, 0.2)	0	0.058 (0.005,0.1)
State 3	0.00001 (0.0, inf)	0.46 (0.2, 0.54)	-0.548 (-1.6,-0.5)	0.08 (0.03, 0.3)	0.00002 (0.00, inf)
State 4	0	0.00009 (0.0, inf)	1.01 (0.6, 1.6)	-1.01 (-1.6, -0.6)	0.0002 (0.0, inf)
State 5	0	0	0	0	0
			OLDER		
State 2	0.086 (0.03,0.2)	-0.185 (-0.3,-0.1)	0.075 (0.02, 0.2)	0	0.024 (0.005,0.1)
State 3	0	0.33 (0.2, 0.54)	-0.942 (-1.68, 0.5)	0.612 (0.2, 1.4)	0.000002 (0.00,inf)
State 4	0	0.000009 (0.0, inf)	1.24 (0.6, 2.5)	-1.38 (-2.6, -0.7)	0.149 (0.05, 0.4)
State 5	0	0	0	0	0

Author's Construct (2023)

Table 8 shows the hazard rates of transition among the age factor levels: youth, old, and older groups. The older and older age groups have a better recovery rate at state 2 (0.0864 and 0.0676) than the youth (0.057). While the old and older age groups have a less and similar rate of change of moving from a mild to a more severe (moderate) state (0.0751 and 0.08574), the youth are more likely (0.0978) to transit to a more severe state than these two groups. Also, the youth have more than twice the (0.1448/0.0588) risk of

transiting into the absorbing state than the elderly and about six (6) times the (0.1448/0.024) risk of entering the absorbing state than the older age group. According to the table, older adults receive less rehabilitation (0.0752) than youth (0.0925). At a moderate state, the youth have about double the chance (0.6434/0.3303) and about 1.4 times the chance (0.6434/0.46 =1.4) of transiting to a less severe state than both the old and the older. Similarly, older and older patients with moderate stroke have no chance of recovering. Finally, a patient with a severe stroke has zero chance of transiting to a less severe state, so older patients with a severe stroke stand a higher probability (0.1491) of moving to the absorbing (death) state than both old and young (0.00000002, 0.000002).

Baseline Transition Intensities for Comorbidity

Baseline transition intensities for comorbidity refer to the rate of moving from one health state to another over a specified period of time, considering the presence of one or more comorbidities. Comorbidities are the presence of one or more additional diseases or disorders co-occurring with a primary disease or disorder. For example, a person with stroke may also have high blood pressure and heart disease, which are comorbidities.

To estimate baseline transition intensities for comorbidity, CTMC models are typically use for large datasets that include information on the health status of individuals, as well as their medical history, demographic characteristics, and other relevant factors. These datasets was obtained from TTH to investigate the behavior of some comorbidity of stroke patients on rehabilitation.

Once the baseline transition intensities for comorbidity have been estimated, they can be used to assess the risk associated with the occurrence and progression of various diseases and disorders. This information may be used by health care providers, and other stakeholders to develop and price health policies, as well as to plan for the future healthcare needs of their patient populations. Whiles, Table 9 displays the baseline transition intensities, Table 10 also compared the transition rate of the various comorbidities.

Table 9: Baseline Transition Intensities for Comorbidity

	Baseline	Comorbidity
State 2- State 1	0.07647 (0.034959, 0.1205)	1.2794 (0.6878,2.371)
State 2- State 2	-0.193 (-0.303534, -0.1416)	
State 2- State 3	0.08732 (0.045535, 0.1651)	0.8845 (0.4359,1.796)
State 2- State 5	0.02923 (0.024375, 0.1284)	0.9071 (0.22202,1.470)
State 3- State 1	0.000000002 (0.00, Inf)	1.0061 (0.00000, Inf)
State 3- State 2	0.443 (0.316, 0.6211)	1.2424 (0.83547,1.817)
State 3- State 3	-0.7218 (-0.9796, -0.5106)	
State 3- State 4	0.2852 (0.159492, 0.5419)	1.6722 (0.47812,2.163)
State 3- State 5	0.000001184 (0.000000, Inf)	2.08084 (0.00000, Inf)
State 4- State 2	0.0000000014 (0.0000, Inf)	0.5344 (0.00000, Inf)
State 4- State 3	1.051(0.688716, 1.6979)	0.7981 (0.48087,1.333)
State 4- State 4	-1.133 (-1.735230, -0.7399)	–
State 4- State 5	0.0795 (0.01668, 0.4329)	0.6872 (0.1034,4.4547)

Author's Construct (2023)

Table 9 shows the baseline probabilities compared with comorbidity effects. The table indicated that comorbidity reduces the recovery rate; a patient with one or more comorbidities is about ten times (0.8845/0.08732) at risk compared to the baseline probability in transiting from mild to moderate state, and has about 45 folds chance of transiting to death (0.9071/0.02923). The hazard rate of comorbidity is about 5.68 times (1.6722/0.2852) the

baseline in transiting from state 2 to 4. Patients without comorbidity recover faster (1.051/0,7981) than patients who surfered from one or more comorbity. Severely rated patients who had one or more comorbidities may die with about 0.6872 hazard rate as compare to patients without any comorbity,

Table 10: Transition Intensities for Comorbidity (hypertensive, hypertensive/diabetes and No comorbidity)

	State 1	State 2	State 3	State 4	State 5
			Hypertensive/Diabetes		
State 2	0.04 (0.02, 0.1)	-0.23 (-0.3, -0.13)	0.094 (0.04, 0.23)	0	0.096 (0.04, 0.21)
State 3	0	0.363 (0.22, 0.58)	-0.625 (-1.02, -0.3)	0.262 (0.10, 0.67)	0
State 4	0	0	1.134 (0.66, 2.7)	-1.417 (-2.7, 0.73)	0.076 (0.01, 0.86)
State 5	0	0	0	0	0
			Hypertensive		
State 2	0.066 (0.03, 0.1)	-0.20 (-0.3, -0.14)	0.086 (0.04, 0.16)	0	0.055 (0.02, 0 .13)
State 3		0.44 (0.31, 0.61)	-0.711 (-0.98,-0.51)	0.266 (0.14, 0.51)	0.00003 (0.0, inf)
State 4	0	0	1.07 (0.68, 1.6)	-1.12 (-1.7, -0.73)	0.051 (0.01, 0.44)

Table 10:Cont.

State 5	0	0	0	0	0
			No Comorbidity		
State 2	0.09	-0.208	0.079	0	0.0313
	(0.05, 0.2)	(-0.36, 0.12)	(0.02, 0.22)		(0.01,0.15)
State 3	0	0.512	-0.9028	0.2710	0.088
		(0.31, 0.92)	(0.09, 0.77)	(0.09, 0.77)	(0.01, 0.57)
State 4	0	0	0.8593	-0.893	0.033
			(0.44, 1.65)	(-1.6, 0.47)	(0.001, 1.8)
State 5	0	0	0	0	0

Author's Construct (2023)

Table 10 shows the effects of hazard rates of transitions influenced by one or more comorbidities. At state 2, patients with no comorbidities have a better rate (0.0983) of total recapture than a patient living with both hypertension and diabetes combined (0.044) or hypertensive patients (0.0658). Thus, patients living with one comorbidity also have a better rate of total recovery (0.0658) than those with hypertension and diabetes (0.044). Also, patients without comorbidities have a lower rate (0.0790) of transiting to a more severe state than patients with one or more comorbidities (0.086, 0.094). Also, patients living with one or more comorbidities (diabetes, diabetes, or hypertension) are more likely to die from stroke (0.096 and 0.0768) than patients without these diseases (0.03134).

A patient with a moderate stroke who has no comorbidities has a (0.5129) chance of progressing to a less severe state than a patient with hypertension or diabetes/hypertension (0.44, 0.3631).The transition rates from state 3 to the more severe state have equal rates for all types of comorbidities.

Finally, patients with severe stroke who have no comorbidities may live longer (0.338) than patients living with one or more comorbidities (0.0509 and 0.07682).

Transition Intensities for Alcohol

Transition intensities for alcohol compared with no alcohol for stroke patients refer to the hazard of moving from one health state to another over a specified period of time, considering the impact of alcohol consumption on health outcomes specifically for individuals who have suffered a stroke. Alcohol consumption has been associated with an increased risk of stroke, and for individuals who have already suffered a stroke, it can further increase the risk of recurrent strokes and other negative health outcomes. The outcome of the transition intensities is shown in Table 11 below.

Table 11: Transition Intensities for Alcohol Compared with No Alcohol

	State 1	State 2	State 3	State 4	State 5
			Alcohol		
State 2	0.074 (0.04, 0.1)	-0.192 (-0.2, -0.1)	0.087 (0.04, 0.16)	0	0.029 (0.01, 0.08)
State 3	0.00004 (0.0, Inf)	0.459 (0.32, 0.63)	-0.711 (-0.9, -0.51)	0.262 (0.13, 0.5)	0.000002 (0.00, Inf)
State 4	0	0.000006 (0.00, Inf)	1.047 (0.68, 1.7)	-1.134 (-1.7, -0.7)	0.0862 (0.02, 0.3)
State 5	0	0	0	0	0
			No Alcohol		
	State 1	State 2	State 3	State 4	State 5

Table 11:Cont.

State 2	0.4055 (0.1, 2.9)	-0.4055 (-2.9, -0.1)	0.000005 (0.000, Inf)	0	0.000002 (0.00, Inf)
State 3	0.000004 (0.0, Inf)	0.000001 (0.00, Inf)	-0.6389 (-3.1, -0.1)	0.3848 (0.04, 3.6)	0.254 (0.03, 0.8)
State 4	0	0.0000001 (0.00, Inf)	0.4945 (0.05, 4.3)	-0.4945 (-4.3, -0.1)	0.000003 (0.0, Inf)
State 5	0	0	0	0	0

Author's Construct (2023)

Table 11 compares the effect of alcohol on stroke patients to patients who do not take alcohol while on rehabilitation. The rate table indicated that patients with no history of alcohol intake at state two (2) have a better rate (0.4055) of transiting to no stroke than patients with a history of alcohol intake (0.07475). Also, patients with an alcohol history retire from recovery (0.087) more than patients with no alcohol history who are transiting to a more severe state (0.000005). Unfortunately, patients with moderate strokes who take alcohol could do better (0.4544) than patients without alcohol (0.00000002). Alcohol-based patients are also less likely to transit to a more severe state (0.2534) as compared to patients without an alcohol history (0.3848). Meanwhile, severe-rated patients with a history of alcohol use have about a 3.6-times (1.671 / 0.4945) chance of transitioning to a less severe state.

Baseline Transition Intensities for Smoking

Once the baseline transition intensities for stroke patients who smoke have been estimated, they can be used in health models to assess the risk associated with the impact of smoking on health outcomes. This information is used by insurance companies, healthcare providers, and other stakeholders to develop and price health products, as well as to plan for the future healthcare needs of stroke patients who smoke.

Table 12: Baseline Transition Intensities for Smoking

	Baseline	Smoking
State 2- State 1	0.02084 (0.000, Inf)	0.2265 (0.0000, Inf)
State 2- State 2	-0.05988 (-Inf, 0.000)	–
State 2- State 3	0.02454 (0.000, Inf)	23700000 (0.00, Inf)
State 2- State 5	0.01450 (0.000, Inf)	2458000000 (0.0, Inf)
State 3- State 1	0.06937 (0.000, Inf)	0.9014 (0.0000, Inf)
State 3- State 2	0.428(0.3065, 0.5975)	2.423 (0.3283,17.883)
State 3- State 3	-0.6864 (-0.9435, -0.4993)	–
State 3- State 4	0.2584 (0.1377, 0.4849)	0.9813 (0.1049, 9.179)
State 3- State 5	0.00000076 (0.000, Inf)	0.0018 (0.0000, Inf)
State 4- State 2	0.00000000005 (0.00, Inf)	2.668 (0.0000, Inf)
State 4- State 3	1.019 (0.6546, 1.585)	2.338 (0.2755,19.846)
State 4- State 4	-1.04(-1.39e+160, -7.735e-161)	–
State 4- State 5	0.02109 (0.000, Inf)	2.996 (0.0000, Inf)

Author's Construct (2023)

Table 12 above indicated the baseline transition rates among patients who sort to smoke in the various states. The rate of transition suggested that smoking has no information as to whether the patients may recover, transit to a more severe or less severe state, or die.

Transition Intensities for Local Treatment

Local treatment of stroke involves the use of techniques such as thrombolysis and mechanical thrombectomy to remove blood clots from the brain and restore blood flow to the affected area. These techniques can help to minimize damage to the brain and improve outcomes for stroke patients.

To estimate the transition intensities for local treatment of stroke, health models typically use large datasets that include information on the local treatment received by stroke patients, as well as their medical history, demographic characteristics, and other relevant factors. The baseline transition rates and the effection of the covariate smoking are presented on Table 13 and Table 14 respectively.

Table 13: Baseline Transition Intensities for Local Treatment

	Baseline	Local Treatment
State 2- State 1	0.0796 (0.04616, 0.1373)	0.9753 (0.3273, 2.907)
State 2- State 2	-0.194 (-0.2841, -0.129)	
State 2- State 3	0.0851 (0.04515, 0.1615)	0.835(0.2356, 2.978)
State 2- State 5	0.02637 (0.0812, 0.8553)	3.417 (0.259, 4.509)
State 3- State 1	0.00000001(0.00, Inf)	0.6914 (0.00000, Inf)
State 3- State 2	0.4368 (0.31809, 0.6075)	0.9553 (0.4844, 1.8780)
State 3- State 3	-0.6895 (-0.9525, -0.499)	
State 3- State 4	0.2526 (0.3135, 0.4857)	0.3536 (0.09125, 1.167)
State 3- State 5	0.00000002 (0.0000, Inf)	0.1239 (0.00000, Inf)
State 4- State 2	0.000000001 (0.00, Inf)	0.6639(0.0000, Inf)
State 4- State 3	0.9956 (0.6392, 1.5357)	0.9466 (0.37432, 2.360)
State 4- State 4	-0.9958 (-1.5368, -0.637)	–
State 4- State 5	0.0002 (0.00000, Inf)	0.000005 (0.00, inf)

Author's Construct (2023)

Table 13 indicates the hazard rates of baseline transition compared with the covariate factor of local treatment. These rates show how local treatment influences the rate of recovery. At state 2, patients who have a

history of local treatment have a higher rate (0.9753) of total recovery than patients who have never had local treatment (0.7961). Local treatment may also speed up recovery by seven times as compared with the baseline rates. At state 3, local treatment may double (0.9538 versus 0.4368) the rate of recovery compared to the baseline rates. Once disease progresses to state 4, patients who have ever had local treatment are less likely to die (0.00005) than the baseline rates (0.0002).

It can also be observed that patients who never seek local treatment have similar characteristics compared with patients who do seek local treatment.

Table 14: Transition Intensities Treatment Type

	State 1	State 2	State 3	State 4	State 5
			Local Treatment		
State 2	0.0799 (0.03,0.1)	-0.204 (-0.33, 0.12)	0.07897 (0.03, 0.19)	0	0.045 (0.02, 0.1)
State 3	0.000008 (0.0, inf)	0.4279 (0.28, 0.65)	-0.5887 (-0.8, -0.4)	0.1607 (0.06, 0.41)	0.00007 (0.00, Inf)
State 4	0	0.0000001 (0.00, Inf)	0.9721 (0.57, 1.6)	-0.9721 (1.61, 0.57)	0.001 (0.0, Inf)
State 5	0	0	0	0	0
			No local Treatment		
State 2	0.08075 (0.03, 0.2)	-0.2255 (-0.3, 0.1)	0.09458 (0.03, 0.23)	0	0.05017 (0.01, 0.14)
State 3	0.000001	0.4487 (0.26, 0.76)	-0.9032 (-1.5, -0.54)	0.0545 (0.2, 1.1)	0.000005 (0.00, Inf)
State 4	0	0.00002 (0.000, Inf)	1.027 (0.47, 2.2)	-1.242 (-2,- 0.6)	0.215 (0.07, 0.6)
State 5	0	0	0	0	0

Author's Construct (2023)

Table 14 above compares the transition rates of patients who combined local treatment and hospital rehabilitation with patients who had only hospital rehabilitation. At state 2 (mild), patients who combined the two treatments achieved a similar total recovery (0.0799) as against patients who did not seek local treatment (0.08075). Patients who combine local treatment are also less likely to transit to a more severe state (0.07897) compared with patients who receive no local treatment (0.09458). A patient seeking local treatment may remain in a mild state for approximately (1 year) 5 visits (1/0.2038) before death (0.045), whereas a patient receiving no local treatment may remain in a mild state for approximately (9 months) 4.43 visits (1/0.2255) before dying at a rate of (0.05017). Moderately rated patients with or without local treatment history may transit to a less severe state with similar transition rates (0.4279, 0.4487). At a severe state, a patient without local treatment will live less than two months (1/1.242) before death (0.2150), whereas local treatment may allow a patient to remain in a severe state for at least two months (1/0.9721) before transitioning to a less severe state.

Right- Hemiparesis Compared with Left- Hemiparesis

Right hemiparesis and left hemiparesis are two common types of motor deficits that can occur after a stroke. Right hemiparesis refers to weakness or paralysis on the right side of the body, while left hemiparesis refers to weakness or paralysis on the left side of the body. Understanding these differences can help insurance companies, healthcare providers, and other stakeholders to develop and price health insurance products, as well as to plan for the future healthcare needs of stroke patients.

Table 15: Right- Hemiparesis Compared with Left- Hemiparesis

	State 1	State 2	State 3	State 4	State 5
			Left Hemiparesis		
State 2	0.08011 (0.05, 0.1)	-0.1746 (-0.2, -0.1)	0.0674 (0.03, 0.15)	0	0.0271 (0.01,0.07)
State 3	0.0000001	0.4058 (0.2, 0.6)	-0.6298 (-0.9, -0.4)	0.224 (0.1, 0.4)	0.0000
State 4	0	0.000007 (0.0, inf)	1.00 (0.62, 1.5)	-1.00 (-1.5,-0.6)	0.000002
State 5	0	0	0	0	0
			Right Hemiparesis		
State 2	0.0788 (0.03, 0.2)	-0.2257 (-0.3,-0.1)	0.1207 (0.05, 0.25)	0	0.026 (0.01, 0.1)
State 3	0.000001	0.4631 (0.3, 0.7)	-0.7643 (-1.1, -0.51)	0.3011 (0.1, 0.6)	0.000
State 4	0	0.000000	0.9948 (0.59, 1.67)	-1.089 (-1.7, -0.6)	0.0944 (0.03,0.3)
State 5	0	0	0	0	0

Author's Construct (2023)

Table 15 compares the hazards rates of transition between patients who had their left-side of the body (arm, leg, or face) paralysed and patients who were paralysed on the right-side. The table indicated that, at mild states, patients who are paralysed on the left or right side have a similar rate of total recovery (0.08011 or 0.0788). Left paralysed patients stayed more than 1.29 times longer (1/0.1746 = 5.73) at the mild state before transition state 1 (total recovery) than right paralysed patients (1/0.2257 = 4.43). Similarly, left-sided paralyses are about twice as likely (0.06738) to transit to a more severe state

than right-sided paralyses (0.1207). Meanwhile, right-paralyzed patients recover faster at moderate levels (0.4631) than left-paralyzed patients (0.4058). Left- or right-sided paralyses have similar probabilities of dying at states 2 and 3. Patients paralysed on the left are at greater risk of dying at state 4 (0.09447) than patients affected by their hand (0.026).

Transition Probability Matrix

With this, the estimated transition probability matrix $P(t)$ for a specific period is extracted. For model 1 (main model), the probabilities for ten years (10) were estimated.

Table 16: Transition Probability Matrix

	State 1	State 2	State 3	State 4	State 4
State 1	1	0	0	0	0
State 2	0.6885	0.0034	0.0008	0.0002	0.3070
State 3	0.6517	0.0043	0.00104	0.0003	0.3426
State 4	0.5958	0.0042	0.00104	0.0003	0.3985
State 5	0	0	0	0	1

Author's Construct (2023)

Table 16 shows the transition probabilities after ten years from the study time. The table revealed that a typical person in state 2, mild stroke, has a probability of 0.3070 of being dead ten years from now, a probability of 0.6885 of total recovery, and a probability of 0.0042 of being alive with a mild, moderate, or severe stroke. Also, an individual in state 4 (severe state) is likely to die ten years from now with a probability of 0.3985, will achieve total recovery with a probability of 0.5958, and has a probability of 0.0057 of surviving with a mild, moderate, or severe stroke.

Model 3: The Mean Sojourn Time

The length of time invested at a transient state before transiting to a less severe state or recovery can be estimated using the mean sojourn time. This is calculated as $\frac{1}{-\hat{q}_{rr}}$, where r^{th} represents the diagonal entry of the calculated transition intensity matrix ($\hat{q}_{rr}$).

Table 17: Model 3: Mean Sojourn Time Estimates

	Estimates	SE	L	U
State 2	5.0946	1.001	3.4663	7.4879
State 3	1.3961	0.2267	1.0156	1.9192
State 4	0.9049	0.1898	0.5998	1.3652

Author's Construct (2023)

Table 17 above shows the estimated average time spent in the state at 2, 3, and 4 before transiting to other states. The results indicated that patients spent on average about 10 months (5.0946; CI = 3.4663, 7.4879) in a mild state before total recovery. Patients with moderate stroke stay for about five (5) months in the moderate state before transiting to the mild state (1.3961; CI =1.0156, 1.9192). Thus, patients admitted with severe stroke or who transited to a severe state do not stay long in this state (0.9049; CI =0.5998, 1.3652).

Survival Plot

Predicting the likelihood of survival for patients with chronic disease in progressively severe states for some time t in the future is significant to the use of multistate in studies of chronic disease. The transition probability matrix $P(t)$ can be used to directly obtain the transition rates. This gives a plot of survival probability against time.

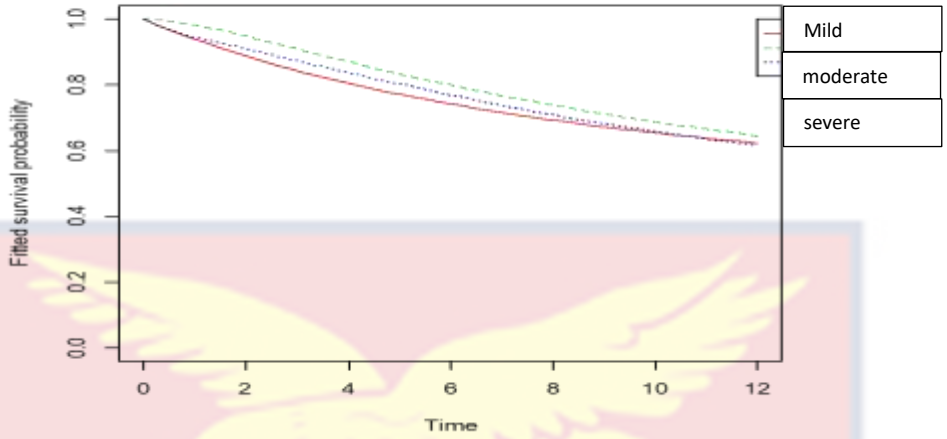

Figure 3: Survival Plot

Author's Construct (2023)

Figure 3 shows that the 2-year survival probability of stroke patients on rehabilitation. At time zero, severe and mild stroke are approximately (0.98) as opposed to 0.92 survival rate with moderate stroke. With a severe stroke, survival probability diminishes slowly to about 0.80 after 12 months (one year) and continues to 0.72 at the end of the 24 months. Moderate stroke indicates a slower diminishing curve. This curve changes from a 0.84 survival rate after one year to about 0.72 at the end of the study period. Finally, mild stroke shows a better survival rate from time zero 0.99 to the survival rate of 0.88 at mid-time and then steadily to 0.75 by the end of the two years.

Model Validation

Observed Frequency Compared with Expected Frequency

Through the use of prevalence counts, we provide a goodness-of-fit test for the suggested model. The prevalence counts offer a free-form empirical measurement of state occupancy. If the model correctly described the data, the predicted state occupancy values should closely match the actual state occupancy values. We would be able to evaluate the fitted model's

general goodness-of-fit by contrasting the observed and forecasted prevalence counts as shown in Table 18 and the observed and expected plots in figure 4.

Table 18: Observed Frequency Compared with Expected Frequency

	Observed Frequency					
	State 1	State 2	State 3	State 4	State 5	Total
0	0	3	15	18	0	36
2	0	10	22	5	0	37
4	1	19	14	2	1	37
6	3	22	5	1	4	37
8	9	13	2	1	8	33
10	10	11	2	0	9	32
12	12	8	1	0	9	30
	Expected Frequency					
	State 1	State 2	State 3	State 4	State 5	Total
0	0.0000	3.000000	15.00000	18.00000	0.0000	36
2	1.4233	13.68754	13.89531	5.560291	2.43347	37
4	3.9558	17.14101	8.796768	2.928585	4.17798	37
6	6.3234	15.84494	5.598535	1.758412	5.37465	35
8	8.2263	13.39063	3.994971	1.174511	6.21350	33
10	9.9055	11.22154	3.040093	0.867884	6.96488	32
12	10.834	8.940524	2.306572	0.647791	7.27048	30

Author's Construct (2023)

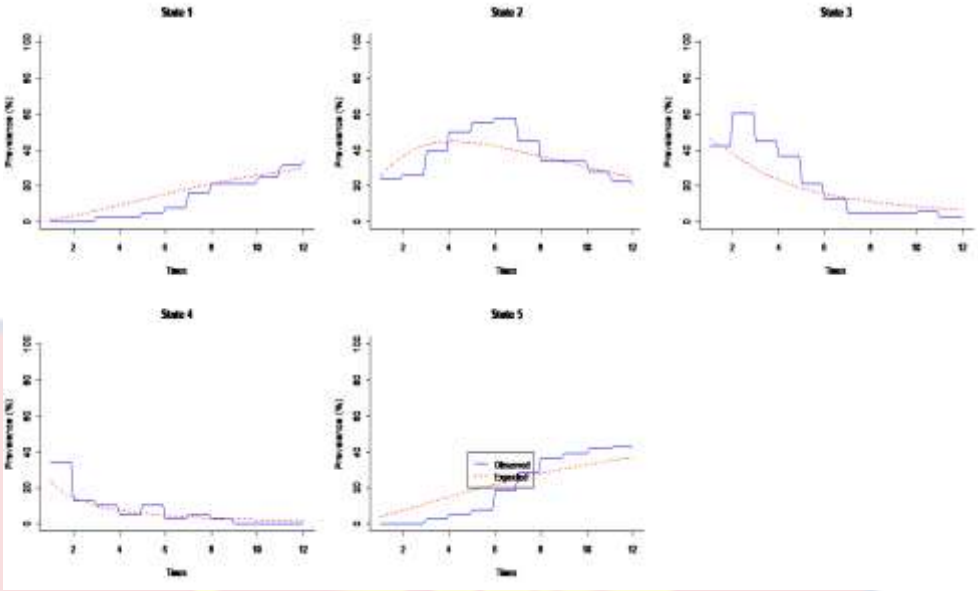

Figure 4: Obseved and Expected Plots
Author's Construct (2023)

Figure 4 above Compares the observed and expected percentages in each state; we noticed that in state one, our model underpredicted the rate of recovery after the time ($t=0$) to time $t=8$. At state 4, the severity of stroke was overestimated before $t=2$. On average, the model predicted well for patients with severe stroke. The rate of death was under-predicted at $t=7$ and over predicted thereof. For a period of four visits, our model under-estimates the hazard rate at (state 2) and over predicted the hazard rate in the next four visits. The model could predict well at state two after $t=8$.

Discussion of Results

The continuous-time Markov chain model in multi-state modelling was used to model the transition rates between the various stroke states. Studies have shown that when data are equally spaced, both the discrete-time Markov chain model and the continuous-time Markov model can perform well. However, CTMC models can perform better when the data set is not equally spaced. Monitoring of patients was taken periodically at two-month discrete

time points; a transition from one state to another is interval-censored. Thirty-seven (37) patients were monitored at two-month intervals for two years.

The purpose of this study is to apply the CTMC model, which will enable us to observe the transition intensities of stroke patients on rehabilitation at some discrete points in time. The model will enable us to determine some risk factors that negatively influence recovery and the effect of comorbidity. This model could inform us about the average length of stay at the various transient states. The model may also serve as a guideline for medical officers on the cost of stroke treatment since the model provided some fair knowledge during treatment.

The results in Table 3 show that the prevalence of stroke among female patients (23, 62.2%) is almost double the number of male patients (14, 37.8%). This may suggest that more females are at risk as compared to males. This is consistent with Edzie *et al*. (2021). Older patients (15, 37.8%) numbered more than the elderly (13, 37.1%). The youth group was the least admitted in the facility (9, 21.6%). About 40.5% of the patients sought local treatment, while another 40.5% may not have received any treatment outside of the health facility. The number of patients living with one or more comorbidities (14 or 8, 18.9% or 40.5%) was higher than the number of patients without comorbidities (15, 37.8%).

The majority of the patients (22, 59.5%) came from the Northern region. Upper East and North East were equally represented (5, 13.5%), four (4) people (10.8%) came from the Savannah region, and only one patient (2.7%) came from the Upper West region. Only two patients (2, 5.4%) never

stopped drinking while in rehabilitation, but the vast majority of patients (35, 94.6%) abandoned their alcohol consumption.

Similarly, more patients (34, 91.9%) quit smoking, and very few patients were addicted to smoking (3, 8.19%). Self-employed persons were more at risk (16, 42.2%), those with no history of employment (10, 27%), civil servants (6, 16.2%), housewives (1, 2.7%), and AGRA Ghana (1, 2.7%).

The transition analysis in Table 4 indicated that 13 patients had total recoveries. There were two (2) transitions from mild to the absorbing state (death), and three (3) from moderate and severe to death. 128 transitions remain in the mild state, 54 remain in the moderate state, and 18 remain in the severe state. This may suggest that many patients admitted with mild stroke did not transit to any other state or that many patients transited from moderate to this state (state 2) within the two-year period.

The transition intensities in Table 5 indicate the transition intensities without covariates to model the progression of stroke. A patient with a mild stroke will remain in this state for about 10 months (1/0.1963) before transiting disease-free state with rate (0.07965) and will never become severe (0) before death (0.03108) if the patient adheres to treatment. This finding is similar to that in Cegarra & Opisso (2020). While patients in a moderate state are more likely (0.4357) to transit to a less severe state, they also have a higher rate (0.2804) of transiting to a more severe state than the other states. Also, patients with severe stroke are more likely (0.0942) to die than patients with moderate (0.0000004) or mild stroke (0.03108). This result does not contradict the literature (Lintu, Shreyas, & Kamath, 2022).

Analysis in Model 2a as shown in Table 7 suggests that female patients have a better rate of transiting to a less severe state (0.8538, 0.3418, and 0.863) than their male counterparts (0.07732, 0.4942, and 1.133).This finding is supported by Shoko *et al*. (2018) CD4 cell count, which shows that the transition from good to bad states is higher in male patients than their female counterparts. Unfortunately, females are more likely to die (0.05483, 0.0029, and 0.1355) than male patients (0.02161, 0.0043, and 0.0523) in all states. This could be because the life expectancy of males is higher than that of females.

The transition rate in model 2b, Table 8 indicated that the age of a stroke patient could retire from recovery about ten (10) times faster than the baseline transition rate (0.8067/0.08457) and has similar rates of transiting to death state (0.4062/0.03108). While the older and older age groups have similar and lower rates of jumping from a moderate to a severe state (0.0873 and 0.6123), the youth are less likely (0.01244) to transit to a severe state than these two groups. Older age with a severe stroke is more likely to die (0.1491) than old age and youth (0.000002, 0.000000002). This result is consistent with the literature (Ieva, Jackson, & Sharples, 2017).

The results in model 2c, Table 10 show that a patient with a moderate stroke and no comorbidity has a (0.5129) chance of transitioning to a less severe state than a patient with hypertension or diabetes/hypertension (0.444, 0.3631). The model also suggested that a patient with a moderate stroke and no comorbidity will, on average, remain in the state for about two months before moving to a less severe state as ($\frac{1}{0.9028} = 1.107$) compared to patients

with one or more comorbidities ($\frac{1}{0.7105}=1.407 or \frac{1}{0.6251}=1.7$).The transition rates from state 3 to the more severe state have similar rates (0.262, 0.2665, and 0.271) for all levels of comorbidity. Finally, patients with severe stroke who have no comorbidities may live longer (1/0.8931) than patients living with one or more comorbidities (1/1.124 and 1/1.417). The results clearly demonstrated that comorbidity decreases the recovery rate. This could suggest that patients with no comorbidities will survive better than patients with one or more comorbidities. This result is similar to Simic-Panic *et al.* (2018); patients with more comorbidity had a worse functional outcome after stroke. Sarfo *et al*. (2018) also indicated that patients with comorbid diabetes and hypertension had a higher crude incidence stroke rate, followed by hypertension and then diabetes. Habibi-Koolaee *et al.* (2018) are consistent with this outcome, finding that hypertension and dyslipidemia significantly increase the risk of ischemic stroke.

The outcome of model 2d, Table 11 gives detailed information on the effect of alcohol on stroke survivors. Patients with no history of alcohol may recover more than five times (0.4055/0.07475) as much as patients with a history of alcohol in a mild state. Findings from the study also indicated that a patient admitted with a severe stroke and a history of alcohol intake has no chance of becoming less severe (1.047), unlike their counterparts with 0.4945 percent chances of moving to a less severe state. This finding is consistent with Palema *et al*. (2010). Their studies have shown that the relationship between alcohol consumption and functional outcome from stroke is sparse.

The transition intensities in model 2e (Table 12) indicated that the covariate smoking has no effect on stroke severity. The baseline intensity for smoking gives hazard rates that are positive one or more, suggesting the covariate has insufficient information for estimating the covariate effect. Several studies have shown a strong positive relationship between cigarette smoking and the risk of stroke recurrence (Sarfo *et al*., 2018; Chen, Li, Zheng, Wang, Xie, Xu, Dai, Gu, Xia, Zhao, Liu, & Xu, 2019; and Bill and Melinda Gates Foundation, 2021). This finding could mean that a stoke patient who previously smoked and quit during rehabilitation may not have any influence on the recovery rate.

The study also estimated the transition ratios of the covariate therapeutic type (local/traditional and modern rehabilitation) as in model 2f (Table 14**)**; these estimates predicted that patients who combined local treatment have a similar recovery rate at a mild state (0.0799) as compares to patients who never had local treatment (0.08075). Meanwhile, patients in a mild state with a combination of local treatment adhere to treatment and are less likely to transit to a more severe state (0.07897) than patients who never subscribed to local treatment (0.09458). Patients with severe stroke who combine local treatment are more likely to transit to a moderate state (0.9721) than patients with no combination of local treatment (1.027 = no sign of recovery). Also, in a severe state with no combination of local treatment, patients are more likely to die (0.05017, 0.2150) compared with patients who combined treatment with non-hospital medication (0.045, 0.000001). These findings are supported by Huang *et al*. (2015): a therapeutic regimen of traditional Chinese medicine (acupuncture) combined with modern

rehabilitation is effective in improving cognition and has the advantages of being simple, convenient, efficient, and inexpensive without severe adverse effects.

Table 15 provides important information on the differences in hazard rates of transition between stroke patients who experience left-side or right-side paralysis. The table suggests that patients who are paralyzed on the left or right side have similar rates of total recovery at mild states. However, left-side paralyzed patients tend to stay longer in the mild state before transitioning to a total recovery state than right-side paralyzed patients.

In addition, left-side paralyzed patients are more likely to transition to a more severe state than right-side paralyzed patients. This finding is consistent with previous research studies (e.g., Jørgensen, Nakayama, Raaschou, & Olsen, 1995) that have reported that stroke patients with right hemiparesis may have a lower risk of developing certain complications, such as depression and cognitive impairment, compared to those with left hemiparesis. On the other hand, left-side paralyzed patients may be more likely to experience language and speech deficits, as well as visual perceptual problems.

The table also shows that right-side paralyzed patients tend to recover faster at moderate levels than left-side paralyzed patients. This finding may have important implications for the development of rehabilitation programs and other interventions that can help stroke patients to recover their motor functions more effectively.

Estimates from model 3 (Table 17**)** show that a patient spent an average of 5 visit points (about 10 months) at state 2 before transiting to state 1, an average of 1.396 visit points (about 3 months) at state 3 before transiting to state 2, and an average of 2 months (SE = 0.8189) at state 4 before transiting to state 3. This may suggest that patients with mild stroke spent a maximum of 15 months (7.489) and a minimum of 6 months (3.16) in a mild state before recovery. This finding may suggest the rate of recovery is faster in state 4 than in state 3. Once a patient transits to state 2, it will take him or her more time to attain state 1. This outcome is similar to a study in the multi-state model for kidney disease progression (Lintu *et al*., 2022).

The survival plot (Figure 3) show 2-year survival rates for severe and moderate strokes of approximately 0.64 as compared to 0.7 for mild strokes. The curves indicate a decreasing trend over time, from t = 0 (0.99), t = 2 (0.88), t = 6 (0.70), and t = 12 (0.64) for severe stroke. Survival of patients with moderate stroke behaves similarly: t = 0 (0.999), t = 2 (0.92), t = 6 (0.8) to t =12 (0.64) for severe stroke, and mild stroke declines from (0.999), (0.9), and (0.7).

Chapter Summary

The purpose of this study is to apply an illness-to-death model (CTMC) that will enable us to observe the transition intensities of stroke patients on rehabilitation at some discrete points of time. We also aim to discover some risk factors that influence recovery and the effect of comorbidity.

We retrospectively obtained stroke data from Tamale Teaching Hospital (TTH). Our data included patients who survived a stroke and were admitted to the medical facility from 2014 to 2019 for stroke rehabilitation. We used CTMC in MSM to observe the transition intensities between the disease states. Continuous Time Markov Chain (CTMC) models can perform better when the data set is not equally-spaced. Monitoring of patients was taken periodically at two-month discrete time points. The transition from one state to another is interval-censored. The model may also serve as a guideline for medical officers on the cost treatment of stroke since the model provided some fair knowledge during treatment.

Results from the study revealed that some covariates contributed (male sex, local treatment, and patients who are free from comorbidity) to early recovery in different states. Some other covariates indicate a decline in stroke recovery (one or more comorbidity, alcohol intake).

The prevalence of stroke among female patients almost doubled the number of male patients. This result is consistent with Edzie *et al*. (2021). Older patients numbered more than old age, the youth was the least admitted in the facility, and about 40.5% of the patients went for local treatment while 40.5% never had any treatment outside the health facility.

The outcome of the transition analysis indicated that patients with mild stroke will remain in this state for about five months before recovery and will never become severe if the patient adheres to treatment. Also, Patients with severe stroke may not survive longer compared to patients with moderate or mild stroke.

Our study also revealed that female patients have a better transition rate to a less severe state than their male counterparts. This finding supports Shoko *et al*. (2018) on CD4 cell count those transitions from a good state to a bad state is higher on male patients than their female counterparts. Unfortunately, females are more likely to die at severe state than males. This is consistent with Agyeman *et al*. (2006).

The age of a stroke patient could retire recovery about ten (10) times than the baseline rate and has the same rates of transiting to death. While old and older age groups have a better chance of transiting to a less severe state and similar rate of moving from mild to a more severe state, the youth have worsened conditions in the more severe state than these two groups. Also, increasing age; 60 or more ($age \geq 60$) admitted with severe stroke have zero chance of survival (increasing age decreases survival rate). Grover et al. (2018) indicated those patients who are age 50 years or more in state two (2) have 4.64 times the rate of moving to state three (3) compared to patients aged below 50 years. Similar studies by Mustapha and Luguterah (2013) on CD4+ cell count of HIV/AIDS patients suggested that a patient have an average of 2.551 count disadvantage for every year older he/she is at the time of diagnosis. Some other researchers (Appelros *et al*., 2003, Liu & McCullough (2012), Nedeltchev *et al*., 2010, Olsen *et al.,* 2011 and Sarfo *et al*., 2018) identified age as a risk factor of stroke.

According to the model in Table 10, a patient with moderate stroke and have no comorbidity has a (0.5129) rate of transiting to a less severe state than to hypertension and diabetes/hypertension (0.44, 0.3631). The model also suggested that a patient who had a moderate stroke with no comorbidity will

remain in the state for an average of about 2 months before moving to a less severe state as compared to patients with one or more comorbidities. Transition rates from state 3 to the severe state have an equal chance for all types of comorbidity. The results demonstrated that comorbidity decreases the recovery rate. This could mean that, patients with non-comorbidity will survive better than patients with one or more comorbidity.

The outcome of transition intensities in Table 11 gives detailed information on the effect of alcohol on stroke survivors. Patients with no history of alcohol may survive more than 4 times than patients with a history of stroke. Findings from our study also indicated patients admitted with severe stroke and have a history of alcohol intake have no information of becoming less severe (1.671) likewise their counterparts with a 0.4945 rate of moving to a less severe state.

The transition intensities in Table 12 indicated that the covariate smoking does not affect stroke severity. The baseline intensity for smoking gives hazard rates to be more than a positive one (1). Thus, the covariate has insufficient information in estimating the hazard rate. Statistics also indicated that patients who previously smoked and quit smoking during rehabilitation may not influence stroke severity.

Estimates from Table 13 shown out that, the transition rates of therapeutic type (local/traditional and modern rehabilitation) predicted that, patients who combined local treatment may not survive longer compared to patients who had only modern therapy. Meanwhile, patients with no combination of local treatment stand tall in total and mild recovery (0.08075, 0.4487 than patients who subscribed to local treatment. Patients with severe

stroke and combined local treatment are more likely to transit to a moderate state (0.9653) than patients with no combination of local therapy.

Patient spent an average of 10 months at state 2 before transiting to state 1, an average of 3 months at state three (3) before moving to state 2, and an average of 2 months at state 4 and then moving to state 3. This result may suggest that patients with a mild stroke spent a maximum of 15 months and a minimum of 7 months at the mild state before recovery. This finding may suggests that the recovery rate is faster at state four (4) than at state 3. Once a patient transit to state 2, it will take the patient more time to attain state 1.

CHAPTER FIVE

SUMMARY, CONCLUSION AND RECOMMENDATIONS

Overview

Longitudinal data analysis of secondary prevention of stroke in Northern Ghana refers to the examination of data collected over a period of time to evaluate the effectiveness of interventions aimed at preventing stroke recurrence in individuals who have already experienced a stroke in the Northern region of Ghana.

In Northern Ghana, where stroke incidence is relatively high, longitudinal studies have been conducted to assess the impact of stroke rehabilitation on secondary stroke prevention. The study typically involved patients who survived a stroke and received medication at TTH from 2014 to 2019. Data was collected at multiple time points to examine the effectiveness of interventions and identify factors associated with stroke recurrence.

The objective of this study is to implement an illness-to-death model to analyse the progression of stroke patients undergoing rehabilitation at specific time intervals. Our goal is to identify potential risk factors that impact recovery and assess the influence of comorbid conditions. Additionally, we aim to investigate the prevalence of comorbidities among stroke patients and evaluate their predictive value at different disease stages. Lastly, we intend to analyse the average duration of patients' stays in various transitional states.

Stroke survivors in Northern Ghana who meet the study's inclusion criteria were identified and recruited for participation. Informed consent is obtained, and relevant demographic and clinical data are collected. At the beginning of the study, baseline data were retrieved from patients medical

records, including participants' socio-demographic information, medical history, stroke characteristics, and risk factor profiles (such as hypertension, diabetes, smoking, etc.).

Collected data is organised, cleaned, and stored securely. Statistical techniques, such as CTMC models, were applied to analyse the data to observed the transition rates over the period and also ascertain the effect of the covariates. These analyses aim to determine the relationship between the interventions (e.g., medication adherence, lifestyle changes, rehabilitation programmes) and stroke recurrence rates while controlling for potential confounding factors.

The findings from the longitudinal data analysis are reported using tables to indicate the transition rates between the various states. The effectiveness of secondary prevention interventions is assessed, and factors associated with stroke recurrence in the Northern Ghana population are identified. These findings can inform future interventions and healthcare policies to improve stroke prevention strategies.

Summary

The purpose of this study is to apply an illness-to-death model that will enable us to observe the transition intensities of stroke patients on rehabilitation at some discrete points in time. We aim to discover some risk factors that influence recovery and the effect of comorbidity. We also aim to determine the prevalence of some comorbidities in stroke patients and examine their predictive values in the various disease states. Finally, we intended to examine the average length of stay of patients in the various

transient states. This will inform medical personnel on the duration of treatment for stroke patients and other possible costs necessary for treatment.

We retrospectively obtained secondary data from the medical unit at TTH. Our data included patients who survived a stroke and were admitted to the medical facility from 2014 to 2019 for stroke rehabilitation. Stroke secondary prevention is considered one of the most successful targets of all stroke managers and modern medicine. The majority of individuals experiencing stroke symptoms seek out their primary care physicians or local treatment before using a direct form of treatment. Though the incidence of stroke has substantially declined in some developed nations due to rigors intervention programmes in high blood pressure control at the population level, the burden of stroke has shifted to developing nations like Ghana. Patients who adhere to treatment measures, as well as successful risk management strategies, in-hospital initiation, and ongoing advice and support from family members and medical officers, may have an early recovery from stroke.

Using CTMC in a multi-state modelling approach, patient records (age, sex, job type, marital status, cigarette smoking, alcohol intake, pre-treatment, severity state, and lifestyle) on stroke were retrieved from the Tamale Teaching Hospital. We provide a literature review on symptoms of stroke, types of strokes, some concepts of stroke, stroke measurement scales, and characteristics of longitudinal studies. We also reviewed previous research on stroke severity and identified some gaps in related work. We finally suggested ways in which we intend to fill these gaps. The theoretical and conceptual frameworks have been fully explained.

The modelling concept included how the transition took place among stroke patients in the various states. We saw how the covariates are incorporated into the main model and the effect of the covariates on recovery. Model diagnoses were done using a goodness-of-fit test to assess how well the observed data fit the expected prevalence count.

Results from the study revealed that our illness-to-death model provided hazards rates between all transient states except the transition from state 2 to state 4. This may suggest patients admitted with a mild stroke all recovered or transited to the absorbing state (death) without moving to state 4. This explained that a patient admitted with a mild stroke who adheres to treatment will recover or advance to a moderate state and will never become severe until death. Some covariates contributed (male sex, local treatment, and patients who are free from comorbidity) to early recovery in different states, while some other covariates indicate a decline in stroke recovery (one or more comorbidities, alcohol intake).

The prevalence of stroke among female patients almost doubled the number of male patients. Older patients numbered more than older patients, the youth was the least admitted in the facility, and about 40.5% of the patients went for local treatment while another 40.5% never had any treatment outside the health facility.

The outcome of the transition analysis indicated that patients with mild stroke will remain in this state for about ten months before recovery and will never become severe if the patient adheres to treatment. Patients with a severe stroke may not survive longer compared to patients with a moderate or mild stroke. Our study also revealed that female patients have a better transition

rate to a less severe state than their male counterparts. The age of a stroke patient could retire recovery about ten (10) times faster than the baseline transition rates. While the older and older age groups have a better chance of transiting to a less severe state and similar rates of moving from a mild to a more severe state, the youth have worsened conditions in the more severe state than these two groups. Also, increasing age (60 or more) decreases the chance of survival (increasing age decreases the survival rate).

A patient with a moderate stroke and no comorbidity has a 0.5129 percent chance of transiting to a less severe state than a patient with hypertension or diabetes and hypertension (0.44 and 0.361, respectively). The model also suggested that a patient who had a moderate stroke with no comorbidity would remain in the state for an average of 2.21 months before moving to a less severe state as compared to patients with one or more comorbidities. The transition rates from state 3 to the severed state have an equal chance for all types of comorbidities. The results demonstrated that comorbidity decreases the recovery rate. This could mean that patients without comorbidities will survive better than patients with one or more comorbidities.

The outcome of model 2d (Table 11) gives detailed information on the effect of alcohol on stroke survivors. Patients with no history of alcohol use may survive more than four times longer than patients with a stroke history. Findings from our study also indicated patients admitted with severe stroke and who have a history of alcohol intake have no indication of becoming less severe (1.671), likewise their counterparts with a 0.4945 rate of moving to a less severe state.

The transition intensities in Table 12 indicated that the covariate smoking does not affect stroke severity. The baseline intensity for smoking gives hazard rates that are greater than a positive one (1). Thus, the covariate provides insufficient information for estimating the hazard rate. Statistics also indicated that patients who previously smoked and quit during rehabilitation may not influence stroke severity.

Estimates from Table 13 show that the transition rates of therapeutic type (local/traditional and modern rehabilitation) predict that patients who combine local treatment may not survive longer compared to patients who have only modern therapy. Meanwhile, patients with no combination of local treatment stand taller in total and mild recovery (0.08075%, 0.4487%) than patients who subscribed to local treatments. Patients with a severe stroke and combined local treatment are more likely to transit to a moderate state (0.9653) than patients with no combination of local therapy.

The average length of time spent in a state The findings revealed that a patient spent an average of 4.5 months at state two before transiting to state 1, an average of 1.4074 months at state three (3) before moving to state 2, and an average of 0.905 months at state four before moving to state 3. This result may suggest that patients with a mild stroke spent a maximum of 6.44 months and a minimum of 3.16 months in the mild state before recovery.

Conclusion

In using CTMC in the MSM approach to modelling the state of stroke patients at Tamale Teaching Hospital, we realised that patients who adhere to treatment measures, as well as successful risk management strategies, in-

hospital initiation, and ongoing advice and support from family members and medical officers, may have early recovery from stroke.

The study revealed that comorbidity is a risk factor for stroke recurrence (patients with one or more comorbidities are less likely to recover compared to patients with no comorbidities). Thus, much attention is needed to be paid to patients with the comorbid disease. This study covered only a few types of comorbidity (diabetes, hypertension, and diabetes). Moreover, the study concludes that alcohol intake, female gender, comorbidity, and increasing age reduce the transition rates over time using the CTMC modelling approach. Therefore, some approved local therapy can be combined with modern rehabilitation therapists.

The research also revealed that CTMC models well estimated the transition rates of stroke patients who were in rehabilitation at the TTH. The model can estimate the transition intensities for all states (1, 2, 3, 4, and 5). The transition rate from state 2 to state 4 is zero (0). Also, the transition from state 2 to 5 is higher (0.0581) than the transition from state 3 to 5 (0.0003).

The study suggests that the recovery rate is faster in more severe states than in less severe states. It must be noticed that patients spent more time in state 2, followed by state 3, and less time in state 4. This implies that patients with mild strokes require more treatment than those in other states in order to fully recover.It is also established that the increasing age of a patient suggests a low survival rate (older patients) with severe stroke are less likely to transit to a less severe state compared to the youth.

Finally, the model assessment (observed and expected frequencies in Table 18) and prevalence plot in Figure 4 suggested that the model (CTMC)

performed well in estimating the severity of stroke among patients on rehabilitation at TTH.

Recommendations

Medical professionals should advise stroke patients not to combine local treatments with rehabilitation. A combination of local treatment may only be sufficient for patients with severe stroke. Thus, patients should seek local treatment from only known registered stroke rehabilitation centres.

Medical professionals should also advise patients who change to a mild state to stick with their treatment plan in order to hasten recovery.Awareness and educational intervention should be focused on long-term rehabilitation so patients do not withdraw from treatment.

Public education on the risk factors for stroke should be emphasised. The Ministry of Health should undertake public education on the risk factors for stroke at the national and community levels.

Suggestions for Further Research

Further research on stroke recovery in Ghana should be carried out to investigate the role of traditional therapy in stroke rehabilitation. Additional studies should focus on the effect of income on transition intensity. In using CTMC models for further studies on transition analysis, the researcher should consider including the misclassification of states in the analysis and separating withdrawal from death as two different absorbing states. Finally, further studies should also consider adding simulation in order to ensure model robustness and performance. This may help in refuting the current studies or otherwise.

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APPENDIX

R CODES FOR MSM ANALYSIS

```
> library(msm)
> data1<-read.csv(file.choose(),header=T)
> attach(data1)
> head(data1)
> statetable.msm(state,PTNUM,data=data1)
> Q<-rbind(c(0,0,0,0,0),
+ c(0.03,0,0.03,0,0.03),
+ c(0.02,0.2,0,0.2,0.2),
+ c(0,0.04,0.14,0,0.2),
+ c(0,0,0,0,0))
> Q.crude<-crudeinits.msm(state~time,PTNUM,data=data1,qmatrix=Q)
> data1.msm<-
msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,deathexact=5)
> data1.msm
Maximum likelihood estimates
```

This will generate the transition rates

COVARIATE EFFECT

```
> data1sex.msm
<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,deathexact=5covari
ates=~sex)
>data1sex.msm<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,deat
hexact=5,covariates=~sex)
```

> data1sex.msm

Call:

msm(formula = state ~ time, subject = PTNUM, data = data1, qmatrix = Q,

covariates = ~sex, deathexact = 5)

Maximum likelihood estimates

Baselines are with covariates set to their means

> qmatrix.msm(data1sex.msm,covariates=list(sex=0))#male

> qmatrix.msm(data1sex.msm,covariates=list(sex=1))#female

>data1age.msm<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,dea

thexact=5,covariates=~age)

> data1age.msm

Maximum likelihood estimates

Baselines are with covariates set to their means

Transition intensities with hazard ratios for each covariate

> qmatrix.msm(data1AGE.msm,covariates=list(AGE=0))#youth

> qmatrix.msm(data1AGE.msm,covariates=list(AGE=1))#old

> qmatrix.msm(data1AGE.msm,covariates=list(AGE=2))#older

>data1Comor.msm<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,

deathexact=5,covariates=~Comor)

> data1Comor.msm

Call:

msm(formula = state ~ time, subject = PTNUM, data = data1, qmatrix = Q,

covariates = ~Comor, deathexact = 5)

Maximum likelihood estimates

Baselines are with covariates set to their means

Transition intensities with hazard ratios for each covariate

>qmatrix.msm(data1Comor.msm,covariates=list(Comor=1))#hypertensive/dia

betes

> qmatrix.msm(data1Comor.msm,covariates=list(Comor=2))#nocomor

>data1alco.msm<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,de

athexact=5,covariates=~alco)

> data1alco.msm

Call:

msm(formula = state ~ time, subject = PTNUM, data = data1, qmatrix = Q,

covariates = ~alco, deathexact = 5)

Maximum likelihood estimates

Baselines are with covariates set to their means

Transition intensities with hazard ratios for each covariate

> qmatrix.msm(data1alco.msm,covariates=list(alco=1))#yes

> qmatrix.msm(data1alco.msm,covariates=list(alco=0))#no

>data1smok.msm<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,d

eathexact=5,covariates=~smoke)

> data1smok.msm

Call:

msm(formula = state ~ time, subject = PTNUM, data = data1, qmatrix = Q,

covariates = ~smok, deathexact = 5)

Maximum likelihood estimates

Baselines are with covariates set to their means

Transition intensities with hazard ratios for each covariate

[Note, to obtain old print format, use "printold.msm"]

```
> qmatrix.msm(data1smok.msm,covariates=list(smok=0))#no
> qmatrix.msm(data1smok.msm,covariates=list(smok=1))#yes
>data1locatrt.msm<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,
deathexact=5,covariates=~locatrt)
> data1locatrt.msm
Call:
msm(formula = state ~ time, subject = PTNUM, data = data1, qmatrix = Q,
covariates = ~locatrt, deathexact = 5)
Maximum likelihood estimates
Baselines are with covariates set to their means
 [Note, to obtain old print format, use "printold.msm"]
> qmatrix.msm(data1locatrt.msm,covariates=list(locatrt=1))#yes
> qmatrix.msm(data1locatrt.msm,covariates=list(locatrt=0))#no
>data1loca.msm<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,de
athexact=5,covariates=~loca)
> data1loca.msm
Maximum likelihood estimates
Baselines are with covariates set to their means
>data1religion.msm<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q
,deathexact=5,covariates=~religion)
> data1religion.msm
Call:
msm(formula = state ~ time, subject = PTNUM, data = data1, qmatrix = Q,
covariates = ~religion, deathexact = 5)
Maximum likelihood estimates
```

Baselines are with covariates set to their means

>data1rehab.msm<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,deathexact=5,covariates=~rehab)

Error in Ccall.msm(params, do.what = "lik", ...) :

numerical overflow in calculating likelihood

>data1stype.msm<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,deathexact=5,covariates=~stype)

Error in solve.default(0.5 * hess) :

system is computationally singular: reciprocal condition number = 2.56211e-21

>data1hemi.msm<msm(state~time,subject=PTNUM,data=data1,qmatrix=Q,deathexact=5,covariates=~hemi)

> data1hemi.msm

Maximum likelihood estimates

Baselines are with covariates set to their means

Transition intensities with hazard ratios for each covariate

> pmatrix.msm(data1.msm,t=60)

> pmatrix.msm(data1.msm,t=12)

> pmatrix.msm(data1.msm,t=36)

> sojourn.msm(data1.msm)

estimates SE L U

> totlos.msm(data1.msm)

State 1 State 2 State 3 State 4 State 5

Inf 0 0 0 Inf

> qmatrix.msm(data1.msm)

```
> prevalence.msm(data1.msm,times=seq(0,36,5))

> prevalence.msm(data1.msm,times=seq(0,12,2))

> options(digits=3)

> prevalence.msm(data1.msm,times=seq(0,12,2))

> plot.prevalence.msm(data1.msm,mintime=0,maxtime=12)
```